Trial Statistical Analysis Plan

c17618627-01

BI Trial No.:	1160.270
Title:	Relative bioavailability of tablet formulation of dabigatran etexilate with and without co-administration of rabeprazole in healthy male subjects (an open-label, single-oral-dose, two-period, single-arm study)
Investigational Product(s):	Pradaxa® (Prazaxa® in Japan), Dabigatran etexilate, BIBR 1048 MS
Responsible trial statistician(s):	[redacted] Address: [redacted] Phone [redacted] Fax: [redacted]
Date of statistical analysis plan:	23 AUGUST 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the Trial statistical analysis plan (TSAP)

Term	Definition / description
AE	Adverse event
BMI	Body mass index
CTP	Clinical Trial Protocol
DE	Dabigatran etexilate
EOT	End of treatment
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PV	Protocol violation
REP	Residual effect period
RPM	Report planning meeting
SD	Standard deviation
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per International Conference on Harmonisation (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 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, randomisation.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The intragastric pH of dabigatran will be explored descriptively.

If there are subjects with considerable high gastric pH, i.e. gastric pH values greater than 5.5 at baseline (1) in reference treatment (dabigatran etexilate alone), ANOVA analyses of primary and secondary endpoints (for the model refer to CTP 7.1.3) will in addition be conducted separately for subjects with considerable high gastric pH at baseline and subjects excluding considerable high gastric pH at baseline as appropriate with respect to number of subjects in the respective groups.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

There is no primary endpoint for efficacy. The primary endpoints will be used as defined in the CTP, Section 5.5.1.1 as PK endpoints.

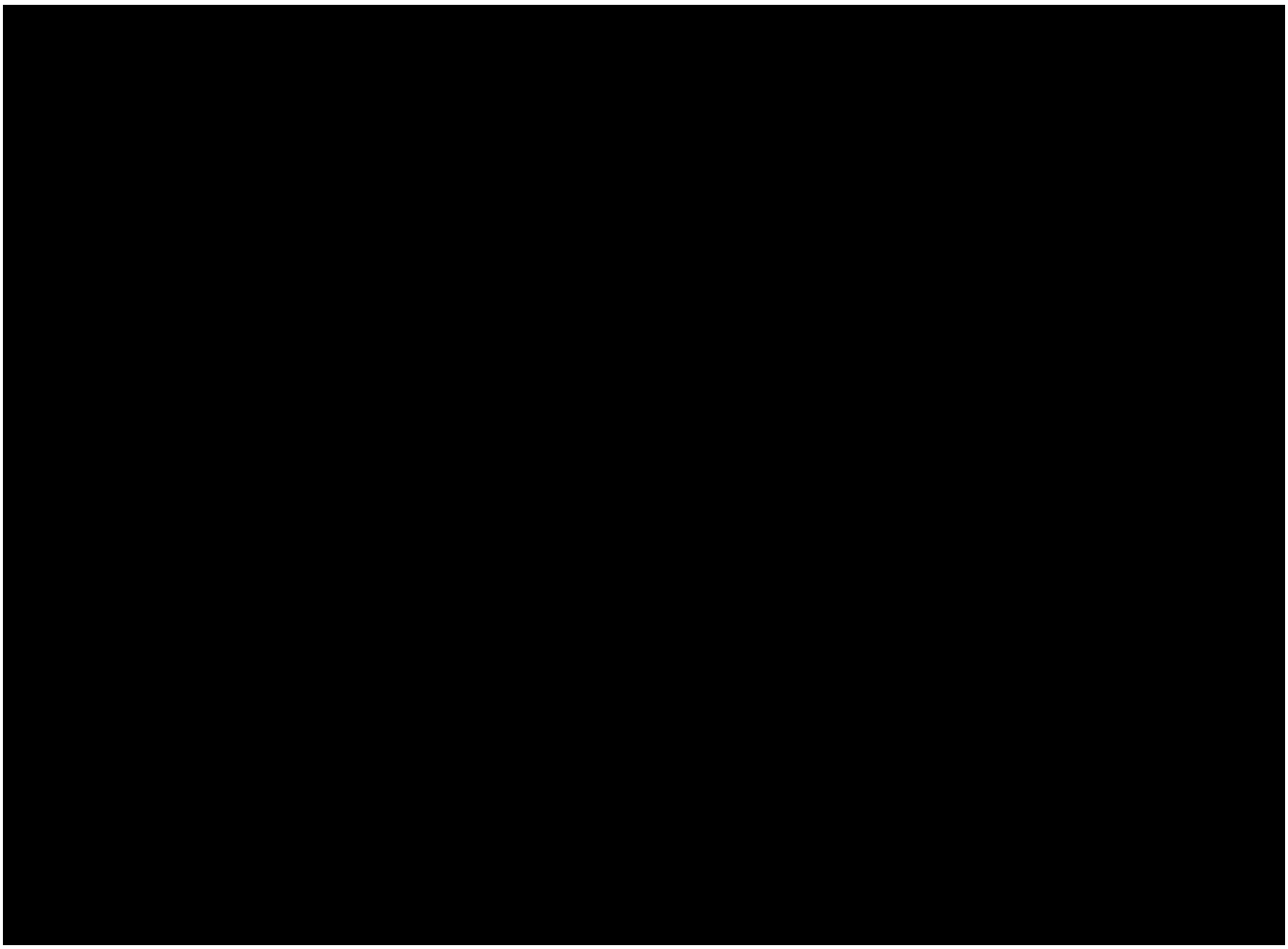
5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

There are no key secondary endpoints in this trial.

5.2.2 Other secondary endpoints

The other secondary endpoints will be used as defined in the CTP, Section 5.5.1.2.



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

6.1.1 Treatment regimens / study intervals

There will be 7 phases in this trial:

screening, treatment period (dabigatran (Period 1), washout, rabeprazole (Period 2) and dabigatran + rabeprazole (period 2)), 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
dabigatran (Period 1)	01	Date of administration in Period 1	Time of administration in Period 1
Washout	02	Date of administration in Period 1	Time of administration in Period 1 + 1 minute
rabeprazole (Period 2)	03	Date of first administration of rabeprazole in Period 2	Time of first administration of rabeprazole in Period 2
dabigatran + rabeprazole (Period 2)	04	Date of first administration of dabigatran in Period 2	Time of first administration of dabigatran in Period 2
Post-treatment	05	Date of last administration in Period 2	Time of last administration in Period 2 + 1 minute
Post-study	99	Date of EOT + 1	0:00

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' (2).

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 (3). 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.

The following Table 6.2: 1 gives the important PVs for this trial.

Table 6.2: 1 Important PVs

Category /Code		Description	Requirements/Comment	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria violated	Inclusion criteria No.1, 2 and 3 Automatically detectable.	None
	A2	Exclusion criteria violated	Automatically detectable.	PKS
B		**Informed consent**		
	B1	Written Informed consent not given	Inclusion criteria No.4 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	Manually detectable.	None
	C3	Incorrect 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 secondary data	PK sample taken too early/too late. Manually detectable.	PKS

KEY: TS = Treated set, PKS = Pharmacokinetic set

6.3 SUBJECT SETS ANALYSED

- Enrolled set (ES):
  This subjects set includes all subjects who enrolled into this trial (i.e., having given informed consent), whether treated or not.
- Treated set (TS):
  This set includes all subjects who were provided with study medication and were documented to have taken at least one dose of investigational treatment.
- Pharmacokinetic set (PKS):
  The PKS includes all treated subjects that provide at least one observation for at least one primary endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints.

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	ES	TS	PKS
Disposition, exposure	X		
Important PVs	X		
Primary endpoints			X
Secondary and further endpoints			X
Safety endpoints		X	
Demographic/baseline endpoints		X	X

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

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 according to the CTP, section 7.4. Additionally, handling information of missing data is shown as follows:

- Missing data and outliers of PK data are handled according to (4).
- Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates"). (5)

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 (4).

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 ENDPOINTS

The analysis will be performed as defined in the CTP, Section 7.3.1.

7.5 SECONDARY ENDPOINTS

7.5.1 Key Secondary endpoints

There are no key secondary endpoints in this trial.

7.5.2 Other Secondary endpoints

The analysis will be performed as defined in the CTP, Section 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 TS.

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 summarisation of AE data, please refer to (5, 6).

The residual effect period (REP) for Dabigatran etexilate (DE) is defined as 3 days after the last administration of DE. Therefore, all AEs which occurred through the treatment phase and throughout the REP are considered as treatment emergent.

The analysis of AEs will be based on the concept of treatment emergent AE. That means that all AEs occurring between the first intakes of dabigatran till 3 days after will be assigned to treatment “dabigatran” (or “reference”) in period 1. In period 2 all AEs occurring between the first intake of rabeprazole until before the intake of dabigatran will be assigned to “rabeprazole“, then after the intake of dabigatran until 3 days later to “dabigatran+ rabeprazole” or “test”. AEs occurring after “dabigatran” but after the REP in period 1 will be assigned to ‘washout’. AEs occurring after “dabigatran+ rabeprazole” but before EOT will

be assigned to ‘post-treatment’. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after EOT will be assigned to 'post-study'.

According to ICH E3 (7), AEs classified as ‘other significant’ needs to be reported and will include those non-serious 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 RPM/database lock (DBL) meeting.

An overall summary of AEs will be presented.

The frequency of subjects with AEs occurring in “dabigatran”, “rabeprazole“ and “dabigatran+ rabeprazole” will be summarised by treatment, primary system organ class and preferred term (MedDRA levels to be displayed in the tables).

Separate tables will be provided for subjects with other significant AEs according to ICH E3 (7), for subjects with significant non-serious AEs (only if these are defined for the project) and for subjects with serious AEs.

The table for the subject with non-serious AEs occurring with incidence in preferred term greater than 5 % will be provided. Additionally, occurred AEs will be listed.

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 and will be based on BI standards (8), descriptive statistics with original values will be provided by period for baseline, on-treatment values and for changes from baseline. Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.
Laboratory values will be compared to their reference ranges and frequency tables will be provided for the number of subjects within and outside the reference range at baseline and the last measurement on treatment. Frequency tables for categorical laboratory values categorised by value at baseline and last value on treatment will be shown.

The last value on-treatment is defined as the last non-missing value observed during ‘dabigatran’ or ‘dabigatran+ rabeprazole’ 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 AEs.

7.8.5 Others

Only descriptive statistics by treatment or PGx phenotype are planned for intragastric pH.

8. REFERENCES

1	Guideline for Bioequivalence Studies of Generic Products: Q & A (original in Japanese), Attachment 1 of Clerical Notification of Pharmaceutical and Food Safety Bureau, dated 29 February 2012.
2	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version; IDEA for CON.
3	*001-MCS-50-413_RD-02*: "Important Manual Protocol Violations Spreadsheet", current version; IDEA for CON.
4	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON;
5	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version IDEA for CON;
6	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", Version 5; 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
8	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", 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	**08-June-17**	[redacted]	None	
Final	**23-Aug-17**		Section 5, 6 and 7	Details for analysis are specified.