Trial Statistical Analysis Plan

c09412381-02

BI Trial No.:	1160.108
Title:	Open label, single arm safety prospective cohort study of dabigatran etexilate for secondary prevention of venous thromboembolism in children from 0 to less than 18 years Including Global Protocol Amendment 6 [c02154816-08], 7 [c02154816-09], and 8 [c02154816-11]
Investigational Product:	Dabigatran etexilate, BIBR 1048 MS
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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse Event of Special Interest
aPTT	Activated partial thromboplastin time
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BRPM	Blinded report planning meeting
BSA	Body surface area
CRNM	Clinically Relevant Non-Major
CTP	Clinical Trial Protocol
DMC	Data Monitoring Committee
dTT	Diluted Thrombin Time
eCRF	electronic Case Report Form
ECT	Ecarin clotting time
eGFR	estimated Glomerular Filtration Rate
EOT	End of Treatment
HPLC	High Pressure Liquid Chromatography
ICH	International Conference on Harmonisation
IPD	Important Protocol Deviation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
MS	Mass Spectrometry
PD	Pharmacodynamics
PKS	Pharmacokinetic Set
PK	Pharmacokinetics
PTS	Post-Thrombotic Syndrome
REP	Residual Effect Period
SAE	Serious adverse event
SD	Standard Deviation
TSAP	Trial Statistical Analysis Plan
VTE	Venous Thromboembolism
WHO	World Health Organization

3. INTRODUCTION

As per International Conference on Harmonisation (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 trial statistical analysis plan (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 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The changes to the statistical analyses are described in protocol amendments. Please refer to latest protocol amendment (Amendment 8, dated 07 Feb 2019).

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

There are no efficacy endpoints. All criteria in this study will be considered as safety endpoints. There are three primary endpoints.

- Recurrence of venous thromboembolism (VTE) at 6 and 12 months
- Major and minor (including clinically relevant non-major (CRNM)) bleeding events (as defined in CTP Section 5.2.1) at 6 and 12 months
- Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months

All primary endpoints will be assessed by qualified clinicians using an appropriate objective method and will be centrally adjudicated by an independent committee.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

This section is not applicable as no key secondary endpoint is defined.

5.2.2 Other secondary endpoints

The following secondary endpoints are defined:

- Occurrence of post-thrombotic syndrome (PTS) at 6 and 12 months
- Pharmacodynamic assessments (central measurement of of dTT (Anti-Factor IIa activity), aPTT and ECT) at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment
- Number of dabigatran etexilate dose adjustments during treatment period (refers to number of patients with dabigatran etexilate dose adjustments during treatment period)

- Incidence of adverse events (AEs), protocol-specified adverse events of special interest (AESI) and serious adverse events

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

This is an open-label single arm prospective cohort study of dabigatran etexilate to evaluate safety in the secondary prevention of venous thromboembolism in paediatric patients. A minimum of 100 paediatric patients are planned to be entered into the trial and be assigned to dabigatran etexilate at a dose (twice daily) based on patient's age and weight according to a nomogram. This includes patients rolling over from study 1160.106, who require secondary VTE prevention and new patients who should have completed treatment for an acute VTE episode. The Data Monitoring Committee (DMC) or Sponsor may decide to keep recruitment open after 100 patients have been recruited, in case additional safety data need to be generated.

The residual effect period (REP) is 3 days after the last trial medication administration.

The following periods will be defined:

- Screening: day of informed consent to time of first dabigatran etexilate administration in trial 1160.108.
- On-treatment: time of first administration of dabigatran etexilate in trial 1160.108 to 3 days (REP) after day of last administration of dabigatran etexilate in trial 1160.108.
- Post-treatment: end of on-treatment period + 1 day up to day of the last follow-up visit, lost to follow-up, death, or consent withdrawn regarding participation in the trial.
- Post-study: last follow-up visit + 1 day up to end of the trial, i.e. the last contact/last information received during the trial.
- Full follow-up: time of first administration of dabigatran etexilate in trial 1160.108 until day of the last follow-up visit, lost to follow-up, death, or consent withdrawn regarding participation in the trial. This treatment period was defined for sensitivity analyses only.

Please note: for patients who had not reached the end of treatment period as defined above at EMA interim data cut-off date, the respective treatment period ends at the cut-off date.

The screening, on-treatment, post-treatment, and post-study periods will be used for the summary and listings of adverse events. The on-treatment and full follow-up periods will be used for descriptive and statistical analysis of primary/secondary/further endpoints.

6.2 IMPORTANT PROTOCOL DEVIATIONS

No per protocol set will be defined for this study, however patients with potentially important protocol deviations (IPDs) will be documented. The following list of potentially IPDs will be used.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Age >=18 years at the time of informed consent / assent	Inclusion criterion 1 not met	None
	A1.2	Previously documented objective diagnosis of VTE, not complete the course of initial VTE treatment for at least 3 months, or not complete study treatment in the 1160.106	Inclusion criterion 2 not met.	None
	A1.3	No presence of an unresolved clinical risk factor requiring further anticoagulation for secondary VTE prevention	Inclusion criterion 3 not met	None
	A2.1	Patients had conditions associated with an increased risk of bleeding	Exclusion criterion 1 met. Details are specified in the protocol Section 3.3.3.	None
	A2.2	Renal dysfunction or requirement for dialysis	Exclusion criterion 2 met. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 for patients aged 12 to < 18 years or eGFR < 80 mL/min/1.73m^2 for patients aged 0 to < 12 years using the Schwartz formula, or requirement for dialysis	None
	A2.3	Active infective endocarditis	Exclusion criterion 3 met.	None
	A2.4	Heart valve prosthesis requiring anticoagulation	Exclusion criterion 4 met.	None
	A2.5	Patients with hepatic disease	Exclusion criterion 5 met.	None
	A2.6	Pregnant or breast feeding females	Exclusion criterion 6 met.	None
	A2.7	Age group 0 to < 2 years with gestational age at birth < 37 weeks or with body weight < 3rd percentile	Exclusion criterion 7 met.	None
	A2.8	Anaemia or thrombocytopenia at screening	Exclusion criterion 8 met.	None
	A2.9	Restricted medication use prior to first dose of study medication	Exclusion criterion 9 met.	
	A2.10	Patients received an investigational drug in the past 30 days prior to screening	Exclusion criterion 10 met (except patients who have completed the treatment period in 1160.106 trial)	None
	A2.11	Allergic / sensitive to any component of the study medication including solvent	Exclusion criterion 11 met. f	None
	A2.12	Patients or parents / legal guardians considered unreliable to participate in the trial per investigator judgment or any condition which would present a safety hazard to the patient based on investigator judgment	Exclusion criterion 12 met.	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 1 date <*Visit 1 date*>	None

Table 6.2: 1 (continued) Important protocol violations

Category / Code		Description	Example/Comment	Excluded from
C		**Trial medication and randomisation**		
	C1.1	Incorrect trial medication taken	Medication kit assigned not matching interactive voice response system (IVRS) assignment, not leading to a change in the assigned treatment. (e.g. wrong dose or formulation of dabigatran etexilate was administered). Wrong dose assigned by investigator.	None
	C2	Non-compliance	Medication compliance of <80% or >120%. Temporary interruption following protocol specified procedures will not be considered as violation.	None
	C3.1	Incorrect dabigatran titration	A second dabigatran titration was performed after one titration attempt failed, or dabigatran titration was performed when it was not required according to protocol.	None
	C3.2	Dabigatran titration not done when required	DE could have been titrated when the trough DE concentration is outside the 50 to <250 ng/mL range.	None
	C3.3	Dabigatran not stopped when plasma trough concentration did not reach therapeutic range after one dose adjustment	Dabigatran not stopped after two confirmed trough concentrations outside 50 to < 250 ng/mL range	None
D		**Concomitant medication**		
	D1	Prohibited concomitant medication use	Restricted concomitant treatments are listed in protocol Section 4.2.2.1 with appropriate exceptions.	None
Z		**Other**		
	Z1	Patients treated with dabigatran etexilate developed renal dysfunction and were not discontinued from DE	Patients with eGFR < 50 mL/min/1.73m^2 twice on dabigatran and trial treatment continued	None
	Z2	Patients with observed recurrent thromboembolic event by appropriate imaging modalities and were not discontinued from DE	Patients with recurrent VTE and not stopped from dabigatran etexilate. Details in protocol Section 3.3.4.1.	None
	Z3	Patients with drug related significant/serious AE or drug toxicity and were not discontinued from DE	Patients with drug related significant/serious AE or drug toxicity and not stopped from dabigatran etexilate. Details in protocol Section 3.3.4.1.	None
	Z4	Patients became pregnant and were not discontinued from DE	Patients become pregnant and not stopped from dabigatran etexilate. Details in protocol Section 3.3.4.1.	None
	Z5	Patients developed active meningitis, encephalitis, or intracranial abscess and were not discontinued from DE	Patients developing active meningitis, encephalitis or intracranial abscess and NOT stopped from dabigatran etexilate. Details in protocol Section 3.3.4.1.	None
	Z6	Use of DE outside the clinical trial		None

This table includes IPDs checked by both automated SAS program and manual reporting. All manual findings should be reported in manual protocol deviation log for team review during medical quality review meeting (MQRM) and blinded report planning meeting (BRPM).

6.3 PATIENT SETS AND ANALYSED

The following analysis sets are defined for the data analysis in this trial:

- Enrolled set: This patient set includes all patients with signed informed consent. The enrolled set will be used for disposition summaries.

- Entered set: This patient set includes all patients with signed informed consent and were eligible to enter the trial, whether treated or not. The entered set will be used for sensitivity analysis of the primary endpoints.

- Treated set: This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. The treated set will be used to assess safety endpoints, demographics and baseline characteristics, and concomitant diagnosis/therapy and medical history.

- Pharmacodynamic set (PDS): This patient set includes all treated patients who provide at least one evaluable PD observation and had no protocol deviations relevant to the evaluation of PD endpoints. The PDS will be used for the PD analyses.

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A summary of the patient sets analysed is provided in the following table:

Table 6.3: 1 Patient sets analysed

Class of endpoint	**Treated set**	**Entered set**		**PDS**	
Primary endpoints	X, Primary analysis	X, Sensitivity analysis			
Secondary endpoints except PD	X				
Demographic/baseline characteristics	X	X			
PK/PD				X	
Other variables except PK/PD	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 data will not be imputed in general. All patients will be followed to collect necessary efficacy and safety information, even if patients discontinue study medication prematurely.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (2).

Missing data and outliers of PK data are handled according to (3).

The repeated measurements are handled according to BI standards (see "Handling, display and analysis of laboratory data") (5).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, baseline value will be the last available measurement taken prior to first administration of dabigatran etexilate in this trial. If baseline measurements are missing for a patient who has completed the treatment period of 1160.106, the measurements from Visit 8 of 1160.106 will be taken as baseline for this trial.

7. PLANNED ANALYSIS

Descriptive statistics for continuous variables will generally be N (number of patients with non-missing values), mean, standard deviation (SD), minimum, median, and maximum. In general, means, medians and SDs will be presented by one more decimal place than the raw data. Minimums and maximums will be presented by the same number of decimal places as the raw data. Geometric means and geometric coefficients of variation will be used in summaries of PK values.

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

There is no hypothesis testing for this trial. Analyses and summaries will be performed by age groups (birth to <2 year, 2 to <12 years, 12 to <18 years) and overall.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Demographic data (including age, sex, ethnicity, and race) and baseline characteristics (including the following measurements at baseline: height, weight, body mass index, body surface area, blood pressure, and pulse rate) will be summarized for the treated set. Baseline disease characteristics, including the previous VTE diagnosis (deep vein embolism, pulmonary embolism, etc.), days since previous diagnosis, and previous VTE treatments, will be summarized for the treated set. The demographic data and baseline characteristics, and baseline disease characteristics will also be listed by patient.

Additional demographic data and baseline disease characteristics tables will be provided for the entered set if the entered set substantially differs from the treated set.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be summarised descriptively. The concomitant medications taken at baseline and those taken while on treatment will be coded using the WHO Drug coding dictionary. These will then be summarized by WHO Drug ATC coding and listed by patient with each medication taken for the treated set.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Compliance since last visit at individual visits collected in the eCRF will be listed, and average overall compliance will be summarized for the treated set. Number and percentage of patients with compliance categories <80%, 80%-120%, and >120% will also be presented.

7.4 PRIMARY ENDPOINTS

There are no primary efficacy endpoints.

The primary analysis for the primary safety endpoints will be performed with the treated set during the on-treatment period.

Frequency and percentage of patients with recurrence of VTE, major and minor (including CRNM) bleeding, and mortality overall and related to thrombotic or thromboembolic events at 3, 6 and 12 months will be summarized descriptively for each age group and overall.

The survival/event-free probability of primary safety endpoints will be provided by Kaplan-Meier estimation with its 95% confidence intervals at above planned time points. The primary safety endpoints will also be analyzed as time-to-event data and summarized by Kaplan-Meier estimates for quartiles of the time to first occurrence of events, given sufficient number of observed events.

Recurrence of VTE at 6 and 12 months
Time to first recurrence of VTE will be analysed using Kaplan-Meier method. Patients, who do not experience recurrent VTE, drop out from the study early, are lost to follow-up, or die from non-VTE related cause will be considered as non-events and censored.

Major and minor (including CRNM) bleeding events at 6 and 12 months
Time to first occurrence of major bleeding event or minor (including CRNM) will be analysed using Kaplan-Meier method. Patients free from major or minor (including CRNM) bleeding event, early drop-outs, lost to follow-ups, and non-bleeding related deaths will be considered as non-events and censored.

Mortality overall and related to thrombotic or thromboembolic events at 6 and 12 months
Time to mortality overall and time to mortality related to thrombotic or thromboembolic event will be summarized separately by Kaplan-Meier method. Early drop outs and lost to follow-ups will be considered as non-events and censored. Non-thrombotic or non-thromboembolic related death will be considered as censored case for mortality due to thrombotic or thromboembolic events.

All primary endpoints will be evaluated by an independent adjudication committee that will confirm or refute outcome events. Adjudicated assessments for the primary endpoints will be used in the primary and subgroup analyses.

Concordance between adjudicated events and investigator-reported events will also be summarized.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Other secondary endpoints

Secondary analyses are planned for occurrence of PTS at 3, 6 and 12 months, pharmacodynamic assessments at Visit 3 and protocol specified time points after each dose adjustment, and number of patients with dabigatran etexilate dose adjustments during treatment period.

- Time to first occurrence of PTS will be analysed using the Kaplan-Meier estimation if number of observed events is sufficient. Descriptive frequency and percentage of patients with PTS at 3, 6 and 12 month will be presented. Patients free from PTS, early drop-outs, lost to follow-ups and deaths will be considered as non-event and censored. The PTS event-free probability will be estimated by Kaplan-Meier curve with its 95% confidence intervals at such time points. Analysis will be performed with the treated set during the on-treatment period

- Pharmacodynamic assessments (central measurement of dTT, aPTT and ECT) at Visit 3 (after at least six consecutive dabigatran etexilate doses) and after at least 3 days following any dabigatran etexilate dose adjustment will be summarized using descriptive statistics.

- Frequency of dabigatran etexilate dose adjustments during on-treatment period will be summarized descriptively. This refers to number of patients with dabigatran etexilate dose adjustment during treatment period because each patient is allowed to have only one dabigatran etexilate dose adjustment.

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report. Summaries will be provided for treated set. Total treatment time (in days) is defined as date of last administration of dabigatran etexilate – date of first administration of dabigatran etexilate + 1. For rollover patients who received dabigatran treatment in 1160.106, their exposure clock starts from first administration of dabigatran etexilate in 1160.108. Number of patients with dose adjustment is analysed as a secondary endpoint and specified in Section 7.5. Descriptive statistics for the dabigatran etexilate dose assigned will be provided for each age group.

7.8 SAFETY ANALYSIS

The analyses for the primary safety endpoints are described in Section 7.4. Safety analyses will be performed on the treated set. Safety analysis will also be performed on the entered set if the entered set substantially differs from the treated set. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

7.8.1 Adverse events

Unless otherwise specified, the analyses of AEs 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.

AEs will be coded with the most recent available version of MedDRA referred to in the footnote of tables and listings.

AE data will be combined in a 2-step procedure into AEs records. In a first step, AE occurrences, i.e. AE entries on the eCRF, 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 (the second occurrence started at the end date of 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

In a second step, AE episodes will be condensed into AE records provided that episodes are reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment.

For further details on summarization of AE data, please refer (2, 6).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all adverse events occurring between first drug intake till 3 days after last drug intake will be assigned to the administered treatment. All adverse events occurring outside the on-treatment period will be summarized in listings only and assigned to 'screening', 'post-treatment', or 'post-study' see Section 6.1. In addition, AEs occurring before first drug intake but worsening in intensity during the treatment period will also be assigned to the administered treatment. For details on the treatment definition, see Section 6.1. Death information will be provided as listings and will include all treatment periods (i.e. also the post-study period).

According to ICH E3 (6), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant AEs with
(i) 'action taken = discontinued' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Trial Leader/Investigator at a Medical Quality Review Meeting.

An overall summary of AEs will be presented.

Frequency of patients with AEs will be summarised by age group, treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant AEs according to ICH E3 (7), for patients with serious adverse events (SAEs), protocol-specified adverse events of special interest (AESIs), for patients with drug related AEs, as well as patients with AEs leading to treatment discontinuation and death. The system organ classes and preferred terms will be sorted by descending order of frequency.

The following are considered as AESI for this trial:

- Hepatic injury defined by the following alterations of liver parameters: An elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample.
- Creatinine value shows a ≥ 2 fold increase from baseline and is above the upper limit of normal.

The system organ classes and preferred terms will be sorted by frequency in a descending order.

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-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
4	*c09149501-01:* "Population pharmacokinetic analysis of dabigatran etexilate using combined data from paediatric and adult studies"; BIRDS.
5	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
6	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials ", current version; IDEA for CON.
7	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	26-JAN-17		None	This is the final TSAP without any modification based on the protocol Version 6.0 dated 30 Nov 2016.
Revised	25-MAR-19		4	Update changes in planned analysis in accordance with the latest protocol amendment.
			5.2.2	Update description of other secondary endpoint regarding PD assessments to be aligned with CTP version 8, dated 10 Sep, 2018.
			6.1	Update definitions of different periods.
			6.2	Update IPD sub-categories according to team discussion.
			6.3	Add definition of enrolled set, , PDS, and PK/PD set.
			7.3	Update calculation of compliance in terms of overall average.
			7.4	Clarify analysis periods for primary and analyses. Update analysis plan of primary endpoints based on BRPM in Dec 2018.
			7.5.2	Update description of other secondary endpoint regarding PD assessments to be aligned with CTP version 8, dated 10 Sep, 2018. Update analysis plan of PTS based on BRPM in Dec 2018. Add description of subgroup analysis.
			7.7	Clarify the exposure clock for rollover patients from 1160.106.
			7.8.1	Complete the second step of AE data processing from AE occurrences to AE records. Update the order of AE display in summary tables.
			8	Update references table.