

Trial Statistical Analysis Plan

c02393794-03

BI Trial No.:	1160.106
Title:	Open-label, randomized, parallel-group, active-controlled, multi-centre, non-inferiority study of dabigatran etexilate versus standard of care for venous thromboembolism treatment in children from birth to less than 18 years of age: The DIVERSITY study. Including Protocol Amendment 2, 3, 4, 5, 6, 7, 8, and 9 [c02102933-09, c02102933-10, c02102933-11, c02102933-12, c02102933-13, c02102933-14, c02102933-15, and c02102933-16].
Investigational Product:	Dabigatran etexilate, BIBR 1048 MS
Responsible trial statistician:	Tel: _____ Email: _____
Responsible trial clinical pharmacokineticist	Tel.: _____
Date of statistical analysis plan:	25 MAR 2019 REVISED
Version:	Revised
Page 1 of 31	
Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.	

	3
	3
	3
	3
10. HISTORY TABLE.....	37

LIST OF TABLES

Table 6.1: 1	Labels of treatments for use in the Clinical Trial Report.....	11
Table 6.2: 1	Important protocol deviations	13
Table 6.3: 1	Patient sets analysed.....	16
Table 10: 1	History table	38

2. LIST OF ABBREVIATIONS

Term	Definition / description
ACI	Applied Clinical Intelligence, LLC
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine-aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate-aminotransferase
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BRPM	Blinded report planning meeting
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CRNM	Clinically relevant non-major (bleeding event)
eCRF	Electronic Case report form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DE	Dabigatran etexilate
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
dTT	Diluted thrombin time
ECG	Electrocardiogram
ECT	Ecarin clotting time
eEOT	Early end of treatment
eGFR	Estimated glomerular filtration rate
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonisation
INR	International normalized ratio
IPD	Important protocol deviation
ISF	Investigator Site File
ITT	Intention-to-treat
IVRS	Interactive voice response system

Term	Definition / description
KM	Kaplan-Meier
LMWH	Low molecular weight heparin
MBE	Major bleeding event
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MQRM	Medical Quality Review Meeting
MS	Mass spectrometry
OLF	Oral liquid formulation
PD	Pharmacodynamics
PK	Pharmacokinetics
PV	Protocol violation
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SEG	Statistical expert group
SOC	Standard of care
TSAP	Trial statistical analysis plan
VKA	Vitamin K antagonist
VTE	Venous thrombotic event/venous thromboembolism
ULN	Upper limit of normal

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 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 including Protocol Amendments 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

Freedom from major bleeding events has been changed from the co-primary safety endpoint to a secondary endpoint, and major bleeding events have been removed from related null hypotheses in the primary analysis in the protocol amendment 6.

Other changes to the statistical analyses are described in protocol amendments. Please refer to latest protocol amendment (Amendment 9, dated 06Feb2019).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The efficacy combined endpoint is the proportion of patients with:

- Complete thrombus resolution and;
- Freedom from recurrent venous thromboembolism (VTE, including symptomatic and asymptomatic, contiguous progression or non-contiguous new thrombus, deep vein thrombosis, pulmonary and paradoxical embolism, thrombus progression) and;
- Freedom from mortality related to VTE.

All components of the primary efficacy endpoint will be centrally adjudicated by an independent blinded 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 Secondary endpoints

The secondary endpoints are:

- Freedom from major bleeding events (MBEs), defined as either fatal bleeding; clinically overt bleeding associated with a decrease in haemoglobin of at least 20 g/L in a 24-hour period; bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system; or bleeding that requires intervention in an operating suite.
- Pharmacokinetic (PK) and pharmacodynamics (PD) assessments at Visit 3 (after at least six consecutive dabigatran etexilate (DE) doses) and after at least 3 days following any DE dose adjustment
- Frequency of dose adjustments (i.e. number of patients with dose adjustment) temporary and permanent discontinuation from therapy (and number of patients with laboratory monitoring requirements for dose adjustment during the treatment phase
- Frequency of switch of type of anti-coagulation therapy (including DE to standard of care (SOC)) (Frequency of patients switching the type of anti-coagulation therapy including DE to SOC and switching from an intended SOC treatment to another)
- Freedom from thrombus progression at end of therapy (day 84 after randomisation or eEOT, whichever comes first) compared to baseline (i.e. proportion of patients free from thrombus progression at end of therapy compared to baseline)
- Assessment of the acceptability of an age-appropriate formulation at end of therapy
- All bleeding events (i.e. proportion of patients with all bleeding events)
- All-cause mortality (i.e. proportion of patients with all-cause mortality)

- All components of the primary efficacy endpoints, including the proportion of patients with complete thrombus resolution, proportion of patients free from recurrent VTE, and proportion of patients free from VTE related death.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

There are two treatment arms in the study: DE using a dosing algorithm or SOC. The assignment of treatment groups will be based on randomization for randomized patient set as defined in [Section 6.3](#). Patients will be allocated to one of the following treatments given below.

Table 6.1: 1 Labels of treatments for use in the Clinical Trial Report

Treatment	Long label	Short label
A	Dabigatran etexilate	DE
B	Standard of care	SOC

Patients switching from DE to SOC before the end of study will be considered as having treatment periods defined below. Patients switching from the original SOC treatment to another SOC will be considered as no change in the treatment group assignment.

The following periods will be defined:

- Screening: day of informed consent to the day prior to first administration of the trial treatment (DE or SOC)
- On-treatment: day of first administration of trial treatment to last administration of trial treatment + 6 days (residual effect period). This on-treatment period will be used for analysis of safety endpoints and adverse events (AEs), as specified in [Section 7.8.1](#).
- 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 withdraw regarding participation in the trial.
- Post-study: For patients not rolled over to the 1160.108 trial, it starts from last follow-up visit + 1 day up to end of the trial, i.e. the last contact/information received during the trial. For patients rolled over to the 1160.108 trial, it starts from last follow-up visit + 1 day in 1160.106 to the date of informed consent in 1160.108.
- Intention to treat: day of randomization up to Day 84 (+ 7), including all observed time on and off trial medication.
- Full follow-up: day of randomization up to day of the last follow-up visit, lost to follow-up, death, or consent withdrawn regarding participation in the trial.

Please note: for patients who had not reached the end of a 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 AEs. The intention to treat, 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

The following table defines the different categories of important protocol deviations (IPDs). The final column describes which IPDs will be used to exclude patients from the different patient analysis sets.

Table 6.2: 1 Important protocol deviations

Category/ Code	Description	Example/Comment	Excluded from
A	Entrance criteria not met		
A1.1	Age \geq 18 years at the time of informed consent / assent	Inclusion criterion 1 not met	None
A1.2	No documented diagnosis of clinically stable VTE per investigator judgment, or not initially treated with parenteral anticoagulation therapy (minimum of 5 to 7 days, but not longer than 21 days)	Inclusion criterion 2 not met	None
A1.3	Anticipated treatment duration with anticoagulants for the VTE episode is less than 3 month, inclusive of the initial parenteral therapy	Inclusion criterion 3 not met	None
A2.1	Patients have 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	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. Females who have reached menarche and are not using a medically accepted contraceptive method per local guidelines.	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	Prohibited or restricted medication use within one week of the first dose of study medication other than medication for prior VTE treatment and P-glycoprotein inhibitors	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.	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

Table 6.2: 1 Important protocol deviations (cont.)

Category/ Code	Description	Example/Comment	Excluded from	
A	A2.13	Patients or parents/legal guardians who are unwilling or unable to undergo or permit repeat of the baseline imaging tests required to confirm thrombus resolution at study day 84 (or eEOT) or in whom repeating such imaging tests at these pre-specified time points may not be medically in the patient's best interest	Exclusion criterion 13 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 was after Visit 1 date	None
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 randomized treatment. (e.g. wrong dose or formulation of DE was administered). Wrong dose assigned by investigator.	None
	C1.2	Randomization not followed	Patients not treated according to the randomized treatment, except treatment switched at a later time	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 DE titration was performed after one titration attempt failed, or DE 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 DE developed renal dysfunction and were not discontinued from DE	Patients with eGFR <50 mL/min/1.73m ² twice on DE and not stopped from DE	None

Table 6.2: 1 Important protocol deviations (cont.)

Category/ Code	Description	Example/Comment	Excluded from
Z2	Patients with observed new thromboembolic event or a clear clinical progression of the baseline VTE and were not discontinued from DE	Patients with new VTE or baseline VTE progression (e.g. based on ISTH guidelines) and not stopped from DE. 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 DE. 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 DE. 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 IMP. Details in protocol Section 3.3.4.1.	None

This table includes IPDs checked by both automated SAS program and manual reporting. All manual findings should be reported in manual IPD log for team review during medical quality review meetings (MQRMs) and blinded report planning meetings (BRPMs).

6.3 PATIENT SETS ANALYSED

The patient sets are defined as:

- **Enrolled set:** includes all patients with signed informed consent. The enrolled set will be used for disposition summaries.
- **Randomized set:** This patient set includes all randomized patients in the treatment groups to which they were randomized, regardless of being treated or not.
- **Treated set:** This patient set includes all patients who were dispensed study medication (DE or SOC) and were documented to have taken at least one dose of study medication.
- **Pharmacokinetic set (PKS):** This patient set includes all dabigatran treated patients with at least one evaluable PK measurement and having no protocol deviations relevant to the evaluation of PK endpoints.
- **Pharmacodynamic set (PDS):** This patient set includes all dabigatran treated patients with at least one evaluable PD measurement and having no protocol deviations relevant to the evaluation of PD endpoints.

Summary of patient sets is provided in the following table:

Table 6.3: 1 Patient sets analysed

Class of endpoint	Randomized set	Treated set	PKS, PDS,
Primary efficacy endpoint	Primary analysis	Sensitivity analysis	
Secondary and other endpoints	Components of efficacy endpoint	Selected secondary endpoints	PK, PD related secondary endpoints
Safety endpoints		X	
Demographic/baseline characteristics	X		

Selected secondary endpoints to be analysed on treated set include all secondary endpoints except for components of efficacy endpoint and PK/PD related secondary endpoints.

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

All patients will be followed to collect necessary efficacy and safety information, even if patients discontinue study medication prematurely.

Missing data will not be imputed in general. Specification regarding missing thrombus assessment is specified in [Section 7.4](#).

For missing or incomplete AE dates, BI internal procedures and guidelines will be followed [\(1\)](#). Handling of missing PK/PD data will be performed according to the BI standard procedures [\(2\)](#).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the last available measurements taken prior to first administration of DE or SOC (same dates are allowed).

7. PLANNED ANALYSIS

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

Geometric means and geometric coefficients of variation will be used in summaries of PK concentration values.

Tabulation 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. A missing category will be displayed if and 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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided for demographics and baseline disease characteristics. Baseline characteristics of the patients' condition will be presented including the type of SOC (low molecular weight heparin, vitamin K antagonists, and fondaparinux), the type of leading index VTE, days since diagnosis of index VTE prior to randomization, characteristics of the index VTE, duration of parenteral anticoagulant treatment prior to randomization, and the types of initial parenteral anticoagulant therapy (unfractionated heparin, low molecular weight heparin, and etc.). The parenteral anticoagulant for initial treatment will also be listed. Other baseline characteristics including patients' baseline activated partial thromboplastin time (aPTT), Ecarin clotting time (ECT) among DE patients, and [international normalized ratio](#) (INR) and anti-factor Xa among SOC patients will be presented in an accompanying listing.

Descriptive statistics for demographics and baseline characteristics will also be presented by the subgroup of age stratum.

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 World Health Organization (WHO) Drug coding dictionary. These will then be summarized by WHO Drug ATC coding and listed by patient with each medication taken.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Average compliance of DE patients and SOC patients will be summarized and listed separately 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

Primary analysis

The primary analysis of the primary efficacy endpoint will be performed on the randomized set following the intention-to-treat (ITT) principle, based on adjudicated data. For example: patients who were originally randomized to DE and later switched to SOC before Day 84, as cases of premature termination of the study medication, will be further followed up per the visit schedule until Day 84.

The analysis period in the primary analysis starts from the time of randomization to the time point of interest, that is, Day 84 \pm 7 days.

- For patients who die or withdraw consent prior to Day 84 – 7 days, the period for the primary analysis ends with the date of trial completion (i.e. the date of death, or the date of consent withdrawal).
- For patients who discontinue treatment prematurely (for example, due to complete thrombus resolution, AE, DE concentration out of target range after one dose modification, and so on), the latest available thrombus assessment up to Day 84 + 7 days will be used for the primary analysis. In particular, thrombus assessment performed after eEOT but before/at Visit 8 for patients switching from DE to SOC will be used for primary analysis. In terms of the recurrent VTE component or VTE-related mortality component, recurrence or death up to Day 84 + 7 days will be used for primary analysis.
- Patients who are still being treated and have not yet reached Day 84 \pm 7 days at time of EMA interim data cut-off will not be included in the analysis

The primary efficacy endpoint contains three components. Given the composite nature of the primary endpoint, each component will be evaluated separately, and a joint outcome of achieving the primary endpoint will be concluded only if all three components are satisfied.

Component 1: free from VTE-related mortality

Patients with VTE-related death occurring between randomization to Day 84 + 7 days will be considered as NOT meeting the endpoint in terms of the component of “freedom from mortality related to VTE”, and therefore will not contribute to the proportion of patients achieving the primary efficacy endpoint.

Component 2: free from recurrent VTE

The presence of recurrent VTE(s) will be examined throughout the study periods. Unscheduled visits would be conducted in case of suspected recurrence of VTE, so the risk of failure to detect recurrent VTE would be minimized. Patients with multiple recurrent VTEs will be regarded equally as patients with a single recurrent VTE, and only the date of first occurrence will be used for analysis.

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- For patients with recurrent VTE(s) from randomization to Day 84 + 7 days, the component of “free from recurrent VTE” will be considered as NOT satisfied.
- For patients WITHOUT ANY recurrent VTE records:
 - If the entire treatment period is completed (Visit 8 available), the component of “free from recurrent VTE” will be considered as satisfied.
 - If patients die (not VTE-related) or withdraw consent prior to Day 84 - 7 days, the period for VTE assessment ends with the date of trial termination (i.e. the date of death, or the date of consent withdrawal). In the primary analysis, we use last-observation-carried-forward (LOCF)², so no record of recurrent VTE will be considered as “free from recurrent VTE”.
 - If patients discontinue treatment prematurely due to reasons other than death or consent withdrawal, they are expected to be followed up for the remainder of planned study visits and will remain in the randomized set. The decision of whether achieving this efficacy endpoint component depends on the timing of their last study visit, if
 - Last study visit¹ took place on or after Day 84 + 7 days and there is no record of recurrent VTE ever, then the component of “free from recurrent VTE” will be considered as satisfied;
 - Last study visit took place before Day 84 + 7 days, then this component will be considered as missing. In the primary analysis, we use last-observation-carried-forward (LOCF)², so no record of recurrent VTE will be considered as “free from recurrent VTE”.
- Patients with VTE recurrence after Day 84 + 7 days will be considered as recurrent VTE free in the primary analysis,

1. Early discontinued patients should be followed up based on IIT principle, so the last study visit could be Visit 9 or further follow-up visit which is available and latest in time.

2. Given minimized risk of not detecting recurrent VTE due to the study design, as well as the low incidence rate of recurrent VTE in the study population, we assume patients free from recurrent VTE until the presence of contradictory evidence - observed VTE recurrence.

Component 3: complete thrombus resolution

Assessment of index VTE status (best overall response) is scheduled on Day 84 ± 7 days (Visit 8) for patients who are alive without an early consent withdraw, regardless of the treatment status (completion or premature discontinuation) at that time.

- The thrombus status assessed at Day 84 ± 7 days will be used for evaluation of this component. If more than one thrombus assessment is available within this time window, the one closest to Day 84 will be adopted. Furthermore, if two index assessments performed within the time window were equally distant from Day 84 (e.g., an early assessment on Day 78 and a late assessment on Day 90), then the thrombus status after Day 84 will be adopted.
- For patients completing the treatment period OR patients terminating treatment early, if the index thrombus assessment during Day 84 ± 7 days is missing, but an early VTE assessment was performed, for instance, at an unscheduled visit or an eEOT visit, the latest available thrombus status will be carried forward (LOCF) in the primary analysis.
- If not any index VTE assessment was performed until Day 84 + 7 days, these patients will be considered as having missing data and NOT meeting the criterion of “complete thrombus resolution”.
- Patients with index VTE assessment performed only once after Day 84 + 7 days will be considered to have missing data and to not achieve the complete thrombus resolution in the primary analysis,

Age group will be used as stratification factor using a Mantel-Haenszel type weighted average of differences with weights as proposed by Greenland and Robins [R09-1299] (3).

The testing hypotheses for the non-inferiority and superiority of the primary endpoint are:

$H_{01}: p_{IC} - p_{ID} \geq 20\%$ vs. $H_{11}: p_{IC} - p_{ID} < 20\%$, where p stands for the proportion of patients meeting the primary endpoint, the subscript C for SOC, and D for dabigatran etexilate.

$H_{03}: p_{IC} - p_{ID} \geq 0$ vs. $H_{13}: p_{IC} - p_{ID} < 0$.

The details of Cochran-Mantel-Haenszel test and SAS code are provided in [Section 9.4](#).

The non-inferiority of DE to SOC will be claimed if H_{01} were rejected. The superiority of DE will be claimed if H_{03} were rejected.

Upon showing non-inferiority for the primary endpoint, superiority test for the primary endpoint will be performed subsequently at one-sided level of 0.05 without multiplicity correction.

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

Major bleeding events (MBEs)

MBEs will be analysed as time-to-event endpoint by Kaplan-Meier method using on-treatment analysis based on adjudicated data and treated set. The proportion of patients free from MBEs at the end of treatment period (84 days (Visit 8) or eEOT) will be provided by Kaplan-Meier estimates for the two treatment arms pooling all age groups. Due to the low event rate of major bleeding, age group stratification will not be considered. The confidence interval of proportion difference will be calculated based on Kaplan-Meier estimates and its variances.

Patients not having MBEs during the on-treatment period and patients who discontinue from the trial prematurely without having major bleeding events will be censored. For patients who have experienced more than one event during the trial, time to the first occurrence of the event will be used for analysis.

In case no MBE was observed in one of treatment arms, where the Kaplan-Meier estimate cannot be calculated, a descriptive table summarizing all MBEs will be provided.

PK/PD assessments

Analysis of standard PK/PD parameters will be performed according to 001-MCS-36-472_RD-01 on PKS, PDS, set as applicable (2).

Scheduled and unscheduled PK and PD data will be analysed separately. Only scheduled PK and PD data will be summarized descriptively. Unscheduled PK and PD data will be listed. As with unscheduled PK and PD data, PK and PD data collected at dose titration visits will be listed separately. The percentage of PK trough results (HPLC-MS/MS) within the target range of 50 to <250 ng/ml and outside target range at Visit 3, while at steady state (after at least six consecutive dabigatran etexilate doses), and following no more than one dose titration (again, at steady state (after at least 3 days following any dabigatran etexilate dose adjustment)) will be presented by formulation, by age group, and for patients treated with the capped dose and with the uncapped dose.

PK parameters: All concentrations will be listed and summarized descriptively. The concentrations will be compared descriptively with the exposure observed in adult patients or healthy subjects previously. PK data from this study along with data from other trials in the dabigatran program will be used to further refine the adult population PK model (7), allowing it to be used for the generation of predictions optimized for paediatric populations. The results of this model refinement will be reported separately.

PD parameters: The following descriptive statistics will be calculated for the PD parameters aPTT, ECT and any additional PD assay: these include, but are not limited to N, arithmetic mean, standard deviation, minimum, median, and maximum. Further, ratios to baseline (i.e. visit 2) for these parameters will be calculated and assessed by descriptive statistics. Dabigatran concentrations derived from dTT will be compared to dabigatran concentrations determined by HPLC-MS/MS. The comparison will be reported separately.

Dose adjustments, switch of therapy, and discontinuation of medication

The number and percentage of patients with dose adjustments (up-titration and down-titration separately), temporary and permanent discontinuation from therapy, and laboratory monitoring requirements for dose adjustment during the treatment phase will be summarized descriptively by treatment arm on treated set. For the DE arm, dose adjustments until the switch of therapy to SOC will be considered.

The number of laboratory monitoring requirements per patient for dose adjustment during treatment phase will be summarised by the number and percentage of patients requiring 1, 2, or more lab monitoring, as well as the mean, SD, min, median, and max of the number of lab monitoring requirements per patient. For the DE arm, lab monitoring requirements prior to the first switch, if any, to SOC will be counted only.

Frequency of patients switching the type of anti-coagulation therapy, including DE to SOC or change from one type of SOC to another (LMWH, VKA, and Fondaparinux) will be provided descriptively by treatment arm on treated set. For the DE arm, only the switch from DE to SOC will be counted, while for the SOC arm, all switches among SOC medication types will be counted. Reasons for switch of therapy from DE to SOC and among SOC types will be summarized. Frequency of DE treated patients with changes in dose and/or formulation type will also be summarized.

Permanent discontinuation from therapy and the reasons will be summarized in the disposition table.

Assessment of acceptability

Assessment of acceptability of an age-appropriate formulation at the end of therapy will be provided descriptively for DE treated patients.

Assessment of acceptability of capsules, pellets and OLF reconstituted with flavoured or unflavoured solvent at Days 3 (Visit 3), 21 (Visit 5) and 84 (Visit 8), or eEOT after randomisation will be summarized descriptively as well. Questions completed by investigator, by parent/legal guardian, and by patients (if old enough per investigator judgement) will be summarized descriptively.

Thrombus progression

Frequency of patients free from thrombus progression at day 84 ± 7 days after randomization (or eEOT, whichever comes first) will be analyzed descriptively by treatment arm and age group. Patients without VTE assessments by this time point will be summarized as well. Mortality related to VTE will be considered as recurrence of VTE.

All bleeding events and all-cause mortality

All adjudicated bleeding events and adjudicated all-cause mortality will be analyzed as time-to-event endpoint using stratified Cox proportional hazard model with treatment as a covariate in the model and age group as the stratification factor. A pooling of age groups might be necessary if no events were observed in certain age group.

Patients that do not experience any bleeding events will be included as censored observations at the date of patients' last visit, the date of death not related to bleeding, or the date of data cut-off, whichever comes first. Patients being alive at the end of observational period will be censored for all-cause mortality at the date of patients' last date known to be alive, or the date of data cut-off whichever comes first. All bleeding events and all-cause mortality based on treated set will be analysed descriptively and by Kaplan-Meier estimates for each treatment arm.

Incidence of bleeding events including MBEs, CRNM, minor bleeding events, and any bleeding events will be presented, as well as incidence of combined endpoint of major and CRNM bleeding events.

Components of efficacy endpoint

All components of the primary endpoint will be analyzed as proportions using adjudicated data as the primary analysis in [Section 7.4](#). Concordance between adjudicated events and investigator-reported events will also be summarized.

The proportion of patients achieving complete thrombus resolution at visit 8, the proportion of patients free from recurrent VTE, and the proportion of patients free from VTE-related death will be provided. Time to VTE-related death will be analyzed by Cox proportional hazard model with treatment as the covariate. Hazard ratio and p-value for the treatment in the model will be reported, and Kaplan-Meier estimates will be provided.

7.7 EXTENT OF EXPOSURE

Only descriptive statistics are planned for this section of the report. Summaries will be provided for treated set. Total exposure (in days) is defined as date of last administration of DE/SOC – date of first administration of DE /SOC + 1, ignoring the temporary interruptions, i.e. intermittent off-treatment periods were considered in the extent of exposure.

For DE treated patients, listings on exposure, including the actual treatment received, starting dose, formulation type, dates of first and last doses, the total treatment time, whether a dose adjustment was done, whether patient switched to SOC, and reason for change will be provided.

For SOC treated patients, listings on exposure, including the SOC treatment type, medication name, dates of first and last doses, the total treatment time, whether a SOC change was done, and reason for change will be provided.

Dose adjustment, interruption and discontinuation are analysed as secondary endpoints and specified in [Section 7.5](#).

The number and percentage of patients with DE trough plasma concentrations in the target range (50 to < 250 ng/mL) and outside target range while on treatment will be presented.

7.8 SAFETY ANALYSIS

The analysis for MBEs is detailed in [Section 7.5](#).

All safety analyses will be performed on treated set during on-treatment period.

7.8.1 Adverse events

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: “Analysis and Presentation of Adverse Event Data from Clinical Trials” [001-MCG-156] [\(4\)](#).

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

All analyses of AEs will be based on the number of patients with AEs (and not on the number of AEs). For this purpose, 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 electronic case report form (eCRF), will be collapsed into AE episodes provided that all of the following applies:

- The same lowest level term was reported for the occurrences;
- 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 occurrences or treatment changed between the onset of 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.

The analysis of AEs will be based on the concept of treatment emergent AEs. All AEs occurring before drug intake will be assigned to ‘screening’. For DE patients not switching to SOC, all AEs recorded between first DE intake until 6 days after the last administration of DE will be assigned to DE on-treatment period. AEs with onset date after that period will be assigned to post-treatment period. For DE patients who switched to SOC, AEs occurred after patients’ last administration of DE plus 6 days and before 6 days after last administration of SOC will be assigned to SOC on-treatment period. For patients in SOC arm, all AEs occurred between the first drug intake of SOC until 6 days after the last administration of any SOC will be assigned to the on-treatment period (regardless of switching between types of SOC treatment). In addition, AEs occurring before first drug intake but worsening in intensity during the treatment period will also be assigned to the administrated treatment. For details on the treatment definition, see [Section 6.1](#).

All AEs (including bleeding) in the on-treatment period will be tabulated. AEs occurring outside the on-treatment period will be summarized in listings only and assigned to ‘screening’, ‘post-treatment’, or ‘post-study’.

According to ICH E3 (5), AEs classified as ‘other significant’ 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 (5), 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 protocol-specified AESI:

- 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.

8. REFERENCES

1	<i>001-MCG-156_RD-01</i> : "Handling of missing and incomplete AE dates", current version; IDEA for CON.
2	<i>001-MCS-36-472_RD-01</i> : "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
3	Greenland S and Robin JM. Estimation of a common effect parameter from sparse follow-up data. <i>Biometrics</i> 1985;41:55-68 [R09-1299]
4	<i>001-MCG-156</i> : "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON.
5	<i>CPMP/ICH/137/95</i> : "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	<i>001-MCG-157</i> : "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
7	<i>c09149501-01</i> : "Population pharmacokinetic analysis of dabigatran etexilate using combined data from paediatric and adult studies"; BIRDS.

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10: 1 History table

Version	Date	Author	Sections changed	Brief description of change
Final	28-APR-2014		None	This is the final TSAP without any modification
Revised	24-AUG-2015			
Revised	25-MAR-2019		Title page	Addition of CTP amendments. Change of trial statistician. Addition of trial clinical pharmacokineticist.
			4, 5.1	MBE has been removed from the co-primary endpoint due to CTP amendment dated Oct 30, 2017.
			5.2	Addition of MBEs to the secondary endpoint.
			5.2.	Update description of other secondary
			6.1	Update definitions of different periods. Explain the effect of EMA interim data snapshot on analysis periods.
			6.2	Update IPD sub-categories.
			6.3	Addition of enrolled set, PKS, set. Update definition of randomized set and treated set, and remove co-primary safety endpoint to be aligned with CTP amendment.
			6.6	Update this section.
			7.1	Clarification of baseline characteristics of patients' condition.
			7.3	Update specification of compliance data.
			7.4	Specification and further clarification for the primary analyses of primary endpoint,

Proprietary confidential information © 2019 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Version	Date	Author	Sections changed	Brief description of change
				including the analysis set, analysis period, strategy of handling missing data for components of primary endpoint.
			7.5.2	Add analysis plan of MBE to the secondary endpoint. Update description of other secondary endpoints to be aligned with CTP amendment.
			7.7	Specification of analysis for extent of exposure.
			7.8	Clarification of analysis for AE, lab data, and ECG. Update definition of AESI. Addition of global assessment of tolerability into 'Other variables'.