Trial Statistical Analysis Plan

c09126655-02

BI Trial No.:	1321.7
Title:	Single dose, open label, uncontrolled, safety trial of intravenous administration of idarucizumab to paediatric patients enrolled from ongoing phase IIb/III clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism.
Investigational Product:	Idarucizumab
Responsible trial statistician:	Phone:
Date of statistical analysis plan:	31 JUL 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Antidrug antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALQ	Above upper Limit of Quantification
ATC	Anatomical Therapeutic Chemical
aPTT	activated Partial Thromboplastin Time
BI	Boehringer Ingelheim
BLQ	Below lower Limit of Quantification
BRPM	Blinded report planning meeting
CRF	Case report form
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
dTT	diluted Thrombin Time
ECT	Ecarin Clotting Time
ICH	International Conference on Harmonisation
IPV	Important protocol violation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NOA	Not Analysed
NOR	No Valid Result
NOS	No Sample Available
PCC	Prothrombin Complex Concentrate
PD	Pharmacodynamics
PDS	Pharmacodynamic set
PK	Pharmacokinetics
PT	Preferred term
REP	Residual Effect Period, after the last dose of medication with measurable drug levels or pharmacodynamic effects still likely to be present
SD	Standard deviation
SOC	System organ class
TBMA	Trial Biomarker Analyst
TCM	Trial Clinical Monitor

Term	Definition / description
TCPK	Trial Clinical Pharmacokineticist
TS	Treated set
TSAP	Trial statistical analysis plan
TSTAT	Trial statistician
TT	Thrombin Time
ULN	Upper Limit of Normal
WHO	World Health Organization

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, randomisation.”

SAS® Version 9.4 or higher will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Sample size is estimated to be approximately 5 patients. Depending on the actual sample size, listings only may be provided while the descriptive summaries specified in the protocol may not be displayed.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoint is the safety of idarucizumab in a paediatric population as assessed by the occurrence of drug-related adverse events (including immune reactions) and all-cause mortality during the trial.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Other Secondary endpoints

- Percent change of coagulation tests (dTT and ECT) at 30 minutes post-dose compared to pre-dose.
- Time to achieve complete reversal of dabigatran effect, based on coagulation tests (dTT and ECT).
- Duration of complete reversal of dabigatran effect sustained at 24 hours post-dose, based on coagulation tests (dTT and ECT).
- Cessation of bleeding (Group A patients only).
- Bleeding status and other clinical conditions that may contribute to bleeding (Group A patients only) during the trial.
- Development of treatment-emergent ADA with cross reactivity to idarucizumab at 30 days post-dose of idarucizumab.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

It is planned to include approximately 5 patients in this trial. All patients will receive idarucizumab (short label: Ida), which will be administered intravenously as two equal consecutive infusions over 5 to 10 minutes each or as two bolus injections no more than 15 minutes apart.

The residual effect period (REP) is defined as 1 day after the last trial medication application. The following treatment period will be defined:

- Screening: day of informed consent to day of first idarucizumab administration. If same day, then the period before first vial administration of idarucizumab.
- On-treatment: time of first administration of idarucizumab to time of last administration of idarucizumab + 1 day.
- Post-treatment: time after last idarucizumab administration + 1 day, to day of end of trial visit (Visit 5) or consent withdraw.

As it may take up to 5 days for some potentially drug related reactions to show up, 5-day REP will also be considered as sensitivity analysis.

6.2 IMPORTANT PROTOCOL VIOLATIONS

No per protocol set will be defined for this study; however patients with potentially important protocol violations (IPVs) will be documented. The following is the list of potentially IPVs.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criterion 2 for Group A or B not met	Patient not currently treated with dabigatran etexilate in the context of a clinical trial with dabigatran etexilate (1160.106 or 1160.108)	PDS
	A1.2	Inclusion criteria 1, 3, and/or 4 for Group A or B not met	Inclusion criteria 1, 3, and /or 4 not met as specified in the protocol.	PDS
	A2	Exclusion criteria not met	Exclusion criteria not met as specified in the protocol	PDS
B		**Informed consent**		
	B1	Informed consent/assent not available/not done	Informed consent/assent date missing	All
	B2	Informed consent/assent too late	Informed consent/assent date <*actual consent/assent date*> was after Visit 1 date <*Visit 1 date*>	None
C		**Trial medication and randomisation**		
	C1	Incorrect amount of trial medication taken	Only one vial or more than two vials of idarucizumab was administered.	None
	C2	Actual dose given and the dose based on patient's body weight do not match	Actual dose given collected in eCRF and the dose based on patient's body weight (see CTP Table 4.1.2: 1) do not match	None

KEY: PDS – Pharmacodynamic set

All categories listed in Table 6.2: 1 will be checked automatically. Additional IPVs may be identified manually during the course of the study and will be assessed during the Medical and Quality Review meetings (MQRM). If the list of IPVs needs to be enlarged, it will be documented in the Blinded Report Planning Meeting (BRPM) / Database Lock Meeting minutes before database lock.

6.3 PATIENT SETS ANALYSED

Two analysis sets will be used for the data analysis in this trial:

- Treated set (TS): includes all patients who received any dose of idarucizumab. The TS will be used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, as well as PK endpoints and ADA.

- Pharmacodynamic set (PDS): comprises all patients in the TS who provided at least one evaluable pre-dose and at least one post-dose observation for PD endpoints or biomarker measures. The PDS will be used for PD endpoint analyses. Note that for different PD endpoints or biomarkers, the number of evaluable patients may be different.

Table 6.3: 1 Patient sets analysed

	Patient set	
Class of endpoint	Treated set	PDS
Primary endpoints	X	
Secondary and further endpoints	Clinical endpoints; idarucizumab PK endpoint*; ADA	Dabigatran PK endpoint; PD endpoints (biomarkers)
Safety endpoints	X	
Demographic/baseline endpoints	X	

* Only if at least one post-dose evaluable blood sample is available.

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

With respect to efficacy and safety evaluations, it is not planned to impute missing values. The reversal of anticoagulation cannot be defined if either the pre-dose or all post-dose coagulation test is missing, or if the pre-dose coagulation test is below the ULN. Patients in such case will be considered as not evaluable for the corresponding biomarker.

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

Handling of missing PK data will generally be performed according to the BI standards (3).

Drug concentration data identified with below the lower limit of quantification (BLQ) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values) with the exception of unbound sum dabigatran. For this analyte, data identified with BLQ following the administration of idarucizumab may be replaced with the lower limit of quantification, until measurable concentrations re-occur.

The appropriate time frame will be decided by the Trial Clinical Pharmacokineticist (TCPK) and described in the CTR.

With respect to pharmacodynamic evaluations it is not planned to impute missing values. However, clotting times may exceed the maximum clotting time of 500s recorded by the coagulometer, indicating the presence of high concentrations of dabigatran, for example in pre-dose idarucizumab samples. If the blood clotting time exceeds 500s, above the upper limit of quantification (ALQ) will be reported. For calculation of reversal of the anticoagulation effect, ALQ values may be replaced by 500s. In that case ALQ values will be discussed on an individual basis within the trial team (including TCM, Trial Biomarker Analyst (TBMA), TCPK and Trial Statistician (TSTAT) and decisions will be documented in the CTR. There are no rules for evaluation. BLQ values as well as pharmacodynamic data identified with no sample available (NOS), no valid result (NOR), and not analysed (NOA) will not be considered.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, baseline value will be the last available measurement taken prior to administration of idarucizumab (same day is allowed).

7. PLANNED ANALYSIS

This trial has a single treatment group with no control group. Approximately 5 patients will be enrolled in this trial. The primary and secondary endpoints will be reported using descriptive statistics or using listings due to limited number of patients in each group. Descriptive statistics will be performed by patient groups (patients having life-threatening or uncontrolled bleeding and those requiring emergency surgery/urgent procedures) and together, when appropriate from a sample size perspective. Statistical inference will not be performed.

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, 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/PD data.

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

If patients entered the trial more than once (i.e. patients need a reversal of the anticoagulant effect of dabigatran again for a new and independent event), each time will be treated as an independent case. The patient will be assigned different patient identification number for each time of enrolment. The cases will be analysed independently as if from different patients. This is only possible for patients from group B.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and baseline characteristics will be summarized descriptively or listed only depending on the number of patients.

7.2 CONCOMITANT DISEASES AND MEDICATION

The concomitant medications taken at baseline and those taken while on treatment will be coded using the WHO Drug coding dictionary. These will be listed by patient.

Listing of patients' exposure to dabigatran prior to entering the trial will be presented, including the time of last dabigatran intake, daily dose and dabigatran indication.

Medical history and baseline disease will be listed, as well as the baseline bleeding assessment.

7.3 TREATMENT COMPLIANCE

Only a listing is planned for this section of the report. The information on the start and end date and time of each vial of idarucizumab and actual administered volume will be provided.

7.4 PRIMARY ENDPOINTS

There is no primary efficacy endpoint.

As the primary safety endpoints, occurrence of drug-related adverse events (including immune reactions) and all-cause mortality during the trial (from the start of dosing until 30 days after the end of dosing) will be listed. Reason of death will be also listed.

Potential specific risks that could be caused by ADA, such as local injection site reactions, systemic hypersensitivity, including anaphylaxis or immune complex disease, are considered as immune reactions, and will be assessed clinically and listed.

As to summaries of other adverse events, refer to Section 7.8.1.

7.5 SECONDARY ENDPOINTS

Secondary endpoints will be listed based on treated set or pharmacodynamic set according to the nature of endpoints.

7.5.1 Key secondary endpoints

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

7.5.2 Other Secondary endpoints

Percent change from baseline of coagulation tests (dTT and ECT) at 30 minutes post-dose will be summarized descriptively or listed only if deemed appropriate.

Reversal of the anticoagulant effect of dabigatran at time t is defined as:

$$\text{Reversal (t)} = \frac{\text{predose coagulation test} - \text{postdose coagulation test at time t}}{\text{predose coagulation test} - \text{ULN}} \times 100\%$$

Values equal to or higher than 100% will be interpreted as complete reversal of the anticoagulant effect. The reversal of anticoagulant activity will be based on central lab measurements and calculated for coagulation tests, dTT and ECT, separately. Reversal cannot be defined for patients with dTT or ECT pre-dose measurement value less than ULN; such patients are considered as not evaluable for reversal related endpoints. The ULN was determined by using data from studies 1321.1 and 1321.2, calculated as the (arithmetic) mean + 2 * standard deviation (SD) by using all data collected prior to the dosing of dabigatran and the data from patients who were on placebo, as well as pre-dose data from idarucizumab alone treatment (as available).

Time to achieve complete reversal will be reported by listing the calculated reversal values at planned time points and using flags to show whether complete reversal is achieved at planned time points.

Duration of complete reversal, defined as the time period from when a patient first achieves complete reversal, up to the earliest time point among the following: middle point between last observation of 100% reversal and subsequent observation, 24 hours post-dose or re-

starting the treatment of dabigatran or other anticoagulation. Duration of complete reversal can be defined only for those patients who achieved complete reversal.

For Group A patients only, the cessation of bleeding within 24 hours will be reported in a listing.

For Group A patients only, bleeding status will be assessed during treatment period and be summarized descriptively or listed only if deemed appropriate. Other clinical conditions that may contribute to bleeding (Group A patients only) during the trial, such as major trauma or the use of antiplatelets, will also be reported.

The blood sample for idarucizumab ADA is scheduled to be collected prior to vial 1 administration and at Day 30 post-dose. If a patient doesn't have ADA pre-dose and has ADA at Day 30, this patient is considered as having treatment-emergent ADA. Development of treatment-emergent ADA with cross reactivity to idarucizumab at 30 days post-dose of idarucizumab will be reported using a binary outcome (Yes/No).

7.7 EXTENT OF EXPOSURE

Two vials of idarucizumab will be administered no more than 15 minutes apart. Number of vials received, the duration of each vial, time between start of first vial to end of second vial will be listed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on 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 adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

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

- All AE attributes are identical ((LLT, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, and outcome).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

For further details on summarization of AE data, please refer to (2, 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 first drug intake till last drug intake + residual effect period (24 hours) will be assigned to the trial medication. In addition, AEs occurring before first drug intake but with worsening in intensity during the treatment period will also be assigned to the trial medication. All adverse events occurring before first

drug intake will be assigned to 'screening' and all adverse events occurring after the residual effect period will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1.

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 = discontinued' 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, including the summaries of related adverse events, serious adverse events and other significant adverse events according to ICH E3 (5), will be presented using data for the entire study period. All AEs including those in the screening, treatment and post-treatment periods will be listed.

No adverse events of special interest (AESI) have been defined for this trial.

7.8.2 Laboratory data

The laboratory data will be listed. Local aPTT test results will be listed separately.

7.8.3 Vital signs

Clinically relevant changes in vital signs and/or physical examination results since baseline/visit 1 must be recorded as an adverse event on the "Adverse Event" eCRF page and will be analysed accordingly. Vital signs will be listed.

7.8.4 ECG

Clinically relevant findings of ECG will be recorded on "Medical History / Baseline Condition" or "Adverse Events" eCRF pages and will be listed accordingly.

7.8.5 Others

Not applicable.

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	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; 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

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**22-JUL-16**		None	This is the initial TSAP with necessary information for trial conduct. This initial TSAP is based on the protocol finalized on 04Feb2016.
Final	**31-JUL-17**		None	This is the final TSAP without any modification. This final TSAP is based on the protocol finalized on 04Feb2016. Changes to the planned analysis are summarized in Section 4 and detailed in the corresponding sections of the SEAP.