Trial Statistical Analysis Plan

c21239352-02

BI Trial No.:	1321.19
Title:	A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures.
Investigational Product:	Idarucizumab, BI 655075
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Date of statistical analysis plan:	08 JUL 2019 SIGNED
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACT	Activated clotting time
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
CI	Confidence interval
CHF	Congestive heart failure
eCRF	electronic case report form
CTP	Clinical trial protocol
CTR	Clinical trial report
DMC	Data Monitoring Committee
dTT	Diluted thrombin time
ECG	Electrocardiogram
ECT	Ecarin clotting time
FFP	Fresh frozen plasma
GI bleeding	Gastrointestinal bleeding
HPLC	High pressure liquid chromatography
ICH	International Conference on Harmonisation
ICH	Intracerebral hemorrhage
Ida	Idarucizumab
iPD	important protocol deviation
KM	Kaplan-Meier

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MQRM	Medical Quality Review Meeting
PCC	Prothrombin complex concentrate
PD	Pharmacodynamics
PDS	Pharmacodynamics set
PK	Pharmacokinetics
PKS	Pharmacokinetics set
RBC	Red blood cell
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SEE	Systemic embolic event
SEG	Statistical expert group
TIA	Transient ischemic attack
TS	Treated set
TSAP	Trial statistical analysis plan
TT	Thrombin time
ULN	Upper limit of normal
VTE	Venous thrombotic event/venous thromboembolism
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 will be used for all analyses.

Pharmacokinetic (PK) and pharmacodynamic (PD) parameters will be calculated using WinNonlin™ software (professional Network version 6.3, Pharsight Corporation, Mountain View, CA 94041-1530, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint is the maximum reversal of anticoagulant effect of dabigatran based on central laboratory determination of diluted thrombin time (dTT) or ecarin clotting time (ECT), at any time point from the end of the first infusion up to 4 hours (planned time, a maximum 30 minutes time window will be allowed) after the completion of the last infusion.

Maximum reversal of the anticoagulant effect of dabigatran is defined as

$$\text{Reversal} = \frac{\text{predose coagulation test} - \text{minimum postdose coagulation test}}{\text{predose coagulation test} - 100\%\ \text{ULN}} \times 100\%$$

Values equal to or higher than 100% will be interpreted as complete reversal of the anticoagulant effect. Patients in the PDS (defined in section 6.3) that have the predose and at least one postdose coagulation test (dTT or ECT) result will be included in the corresponding analysis. The definition of reversal will also apply to central testing of biomarkers activated partial thromboplastin time (aPTT) and thrombin time (TT).

The values of the upper limit of normal (ULN) are determined using data from 1321.1 and 1321.2 as shown in table 5.1: 1.

Table 5.1: 1 Upper limit of normal for PD/biomarker parameters

	dTT [s]	ECT [s]	aPTT [s]	TT [s]
ULN	35.54	41.26	39.80	14.22

5.2 SECONDARY ENDPOINTS

The same secondary endpoints will be analyzed as defined in the CTP, section 2.1.3, with a few clarification remarks.

Secondary efficacy endpoints include:

- Time to cessation of bleeding (for Group A only) since the first infusion up to 24 hours after the completion of the second infusion. The bleeding status will be assessed before and at several time points after treatment.

- Occurrence of major bleeding (for Group B only) intraoperatively and up to 24 hours post-surgery.

- Minimum unbound sum (free) dabigatran concentrations at any time point since the end of the first infusion up to 4 hours (planned time) after the completion of the last infusion ($C_{min,1}$). A maximum 30 minutes time window will be allowed. Samples collected later than 4.5 hours after the completion of the last infusion will not be included in analysis of this endpoint.

- Reversal of anticoagulation as measured by aPTT and TT, at any time point since the end of the first infusion up to 4 hours (planned time) after the completion of the last infusion. A maximum 30 minutes time window will be allowed. Samples collected later than 4.5 hours after the completion of the last infusion will not be included in analysis of this endpoint.

Secondary safety endpoints include:

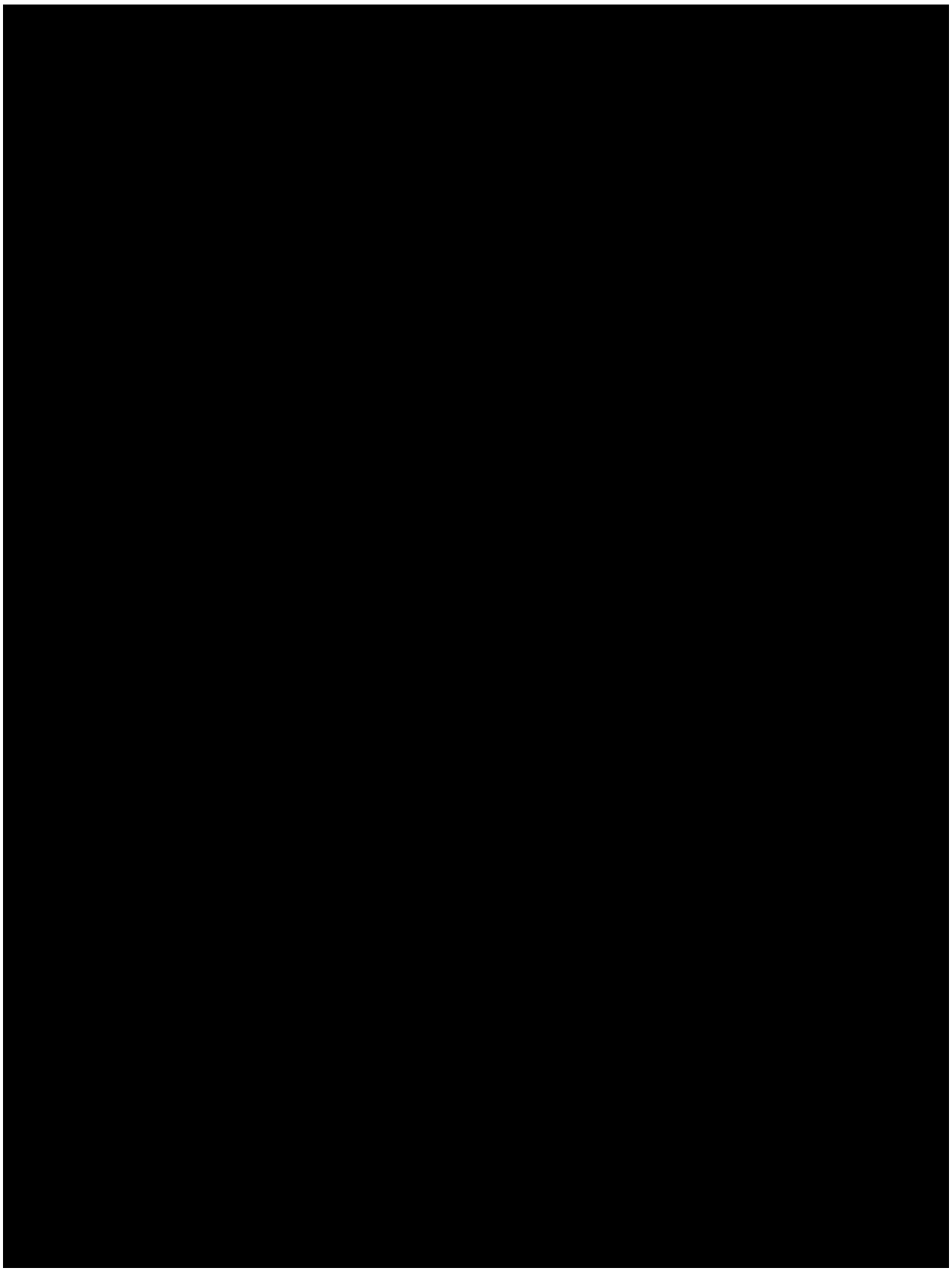
- Numbers of patients with adverse events including local tolerability since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion

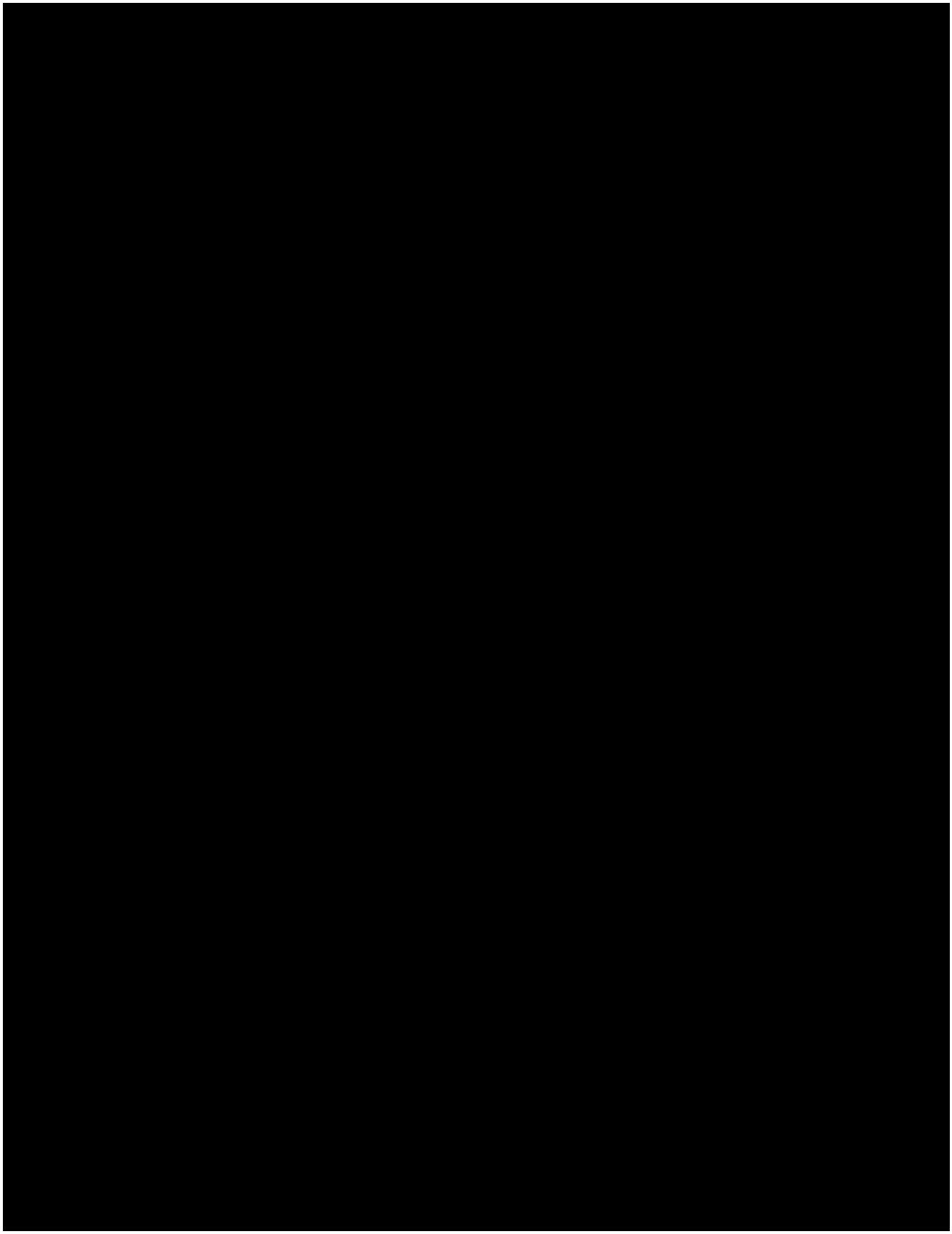
- Numbers of patients with serious adverse events since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion

- Numbers of patients with adverse reactions (adverse events related to treatment) since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion

- Number of patients with immune reactions assessed by AE collection since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion. Immune reactions refer to hypersensitivity identified by narrow SMQ 20000214 and those identified by MedDRA preferred terms pyrexia, malaise, urticaria, pruritus, arthralgia, rash.

- Number of patients with thrombotic events (ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism) since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion. The thrombotic events will be coded using MedDRA based on reported AEs and identified by narrow SMQs 20000081 “embolic and thrombotic events” and 20000047 “myocardial infarction”.





- C_4 (the concentration of unbound sum dabigatran 4 hours after administration)
- C_{12} (the concentration of unbound sum dabigatran 12 hours after administration)
- C_{24} (the concentration of unbound sum dabigatran 24 hours after administration)

Additional pharmacokinetic parameters for sum dabigatran and unbound sum dabigatran may be calculated as appropriate.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

It is planned to include about 20 patients in this trial. All patients will receive idarucizumab (short label: Ida).

The following treatment period will be defined:

- Screening: day of informed consent to start time of the first administration of idarucizumab. If on the same day, then the period before the first administration of idarucizumab.

- On-treatment: start time of the first administration of idarucizumab to 5 days after the end time of the last administration of idarucizumab.

- Post-treatment: 5 days after the end time of the last administration of idarucizumab to day of the end of study visit (visit 5) or consent withdraw.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Table 6.2: 1 Handing of important protocol deviations (iPDs)

Category/ Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Inclusion criteria 1 for Group A or B not met	Patient < 18 years at screening	PKS/PDS
	A1.2	Inclusion criteria 3 for Group A or B not met	No signed and dated written informed consent prior to admission to the trial	All
	A1.3	Inclusion criterion 4 for Group A or B not met	Patient not currently taking dabigatran etexilate	PKS/PDS
	A1.4	Inclusion criteria 5A for Group A or Inclusion criteria 5B for Group B not met	No overt bleeding requiring a reversal agent for Group A or no condition requiring emergency surgery or invasive procedure where adequate hemostasis is required for Group B	PKS/PDS

Table 6.2: 1 (continued) Handing of important protocol deviations (iPDs)

Category/ Code		Description	Requirements	Excluded from
	A2	Exclusion criteria met	Met exclusion criteria as specified in the protocol	PKS/PDS
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent late	Informed consent date <*actual consent date*> was after Visit 2.1 date <*Visit 2 date*>	None
C		**Trial medication and randomization**		
	C1	Incorrect trial medication taken	Only one vial or more than two vials (except for required repeated treatment) of idarucizumab was administered.	None

All categories will be checked automatically. This list will be updated if additional important protocol deviations are detected during the trial conduct.

6.3 PATIENT SETS ANALYSED

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

- Screened set (SCR): include all patients who were screened for this trial with informed consent given.

- Treated set (TS): include all patients who are administered with idarucizumab. The TS will be used to assess safety, clinical endpoints, demographics and other baseline characteristics as well as concomitant diagnosis/therapy and medical history.

- Pharmacokinetic set (PKS): comprise all patients in the TS who provided at least one PK endpoint. The PKS will be used for all PK analyses. Note that for different PK endpoints, the number of evaluable patients might be different.

- Pharmacodynamic set (PDS): comprise 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 the primary efficacy endpoint and all

PD/biomarker endpoints. Note that for different biomarkers or PD endpoints, the number of evaluable patients might be different.

Table 6.3: 1 Patient sets analysed

	Patient Set			
Class of endpoint	SCR	TS	PKS	PDS
Primary endpoint				X
Secondary [redacted] efficacy endpoints		Clinical endpoints	PK endpoints	PD endpoints
Secondary [redacted] safety endpoints		X		
[redacted]	[redacted]			
Disposition	X			
Demographic/baseline endpoints		X		

[redacted]

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. 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 100% ULN. Patients in such cases will be considered as not evaluable for the corresponding biomarker.

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, 3).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline values will be the last measurements taken prior to the administration of the first vial of idarucizumab (same day is allowed). If not available, the values reported at the screening visit will be taken as baseline values. For lab values, baseline is the one observed closest but prior to idarucizumab administration.

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, 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.

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. 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.

In rare cases, if patients enter the trial more than once (i.e. patients need antidote 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.

If a patient receives more than 5g idarucizumab under a single index event, the patient will be assigned a different patient number each time the patient receives an additional 5g idarucizumab and the data collected since the second 5g dose will be associated with subsequent patient number(s) other than the original patient number at enrolment. The demographic and baseline characteristics will be summarized per individual patient, i.e., for these patients, demographic and baseline characteristics from the original patient number will be used. For the analyses of efficacy endpoints, only data collected under the original patient number at enrolment will be included. Efficacy introduced by more than 5g idarucizumab will be described/discussed separately. PK/PD parameters will also be reported separately. For the analyses of safety endpoints, data will be pooled together and presented in summary tables as if only one patient number is used. Some rules will be followed for listings of raw data.

- For baseline and demographic data, patients will be listed once under the first patient number.
- For individual efficacy data, all listings will only show data collected under the first patient number.
- For individual safety and lab data, all listings will show combined data collected under all patient numbers used, identified by the first patient number.

- The following efficacy and safety listings will be repeated to show information collected under all patient numbers, in a sequence without combining.
    - Reasons for all surgeries
    - All bleeding information
    - Individual patient central lab and dabigatran concentration

    - Patients with adverse events by group, primary system organ class and preferred term

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be provided for demographics and baseline characteristics.

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.

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

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. The proportion of patients received one, two or partial vials of idarucizumab will be provided.

7.4 PRIMARY ENDPOINT

For the primary endpoint, the median and 1st, 5th, 10th and 25th percentile of the calculated maximum reversal of the anticoagulation effect among all evaluable patients will be calculated, using each coagulation test separately (ECT and dTT). The 95% confidence interval for median and the percentiles will be calculated based on distribution-free method. Detailed SAS code is included in section 9.1.

Reversal cannot be defined for patients with biomarker test (dTT, ECT, aPTT or TT) pre-dose value less than 100% ULN (not evaluable).

7.5 SECONDARY ENDPOINTS

Secondary endpoints will be analysed based on TS, PKS or PDS according to the nature of 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

Time to cessation of bleeding (for Group A only) since the end of first infusion up to 24 hours after the completion of second infusion will be summarized descriptively for patients (by ICH and non ICH patients if feasible based on sample size) whose bleeding is assessable within 26 hours (assessment at 24 hours with up to 2 hour time window allowed by protocol). ICH patients will not be included in this analysis if no follow-up CT scans are available. For non-ICH patients, patient who dies within 26 hours will be censored at the time of death, and all others censored at 24 hour if they do not stop bleeding prior to 26 hours. Median, 25th and 75th percentile of time to cessation of bleeding will be estimated by Kaplan-Meier method. Probability of stopping bleeding at landmark times (1, 2, 3, 4, 12 and 24 hours, etc.) will be provided.

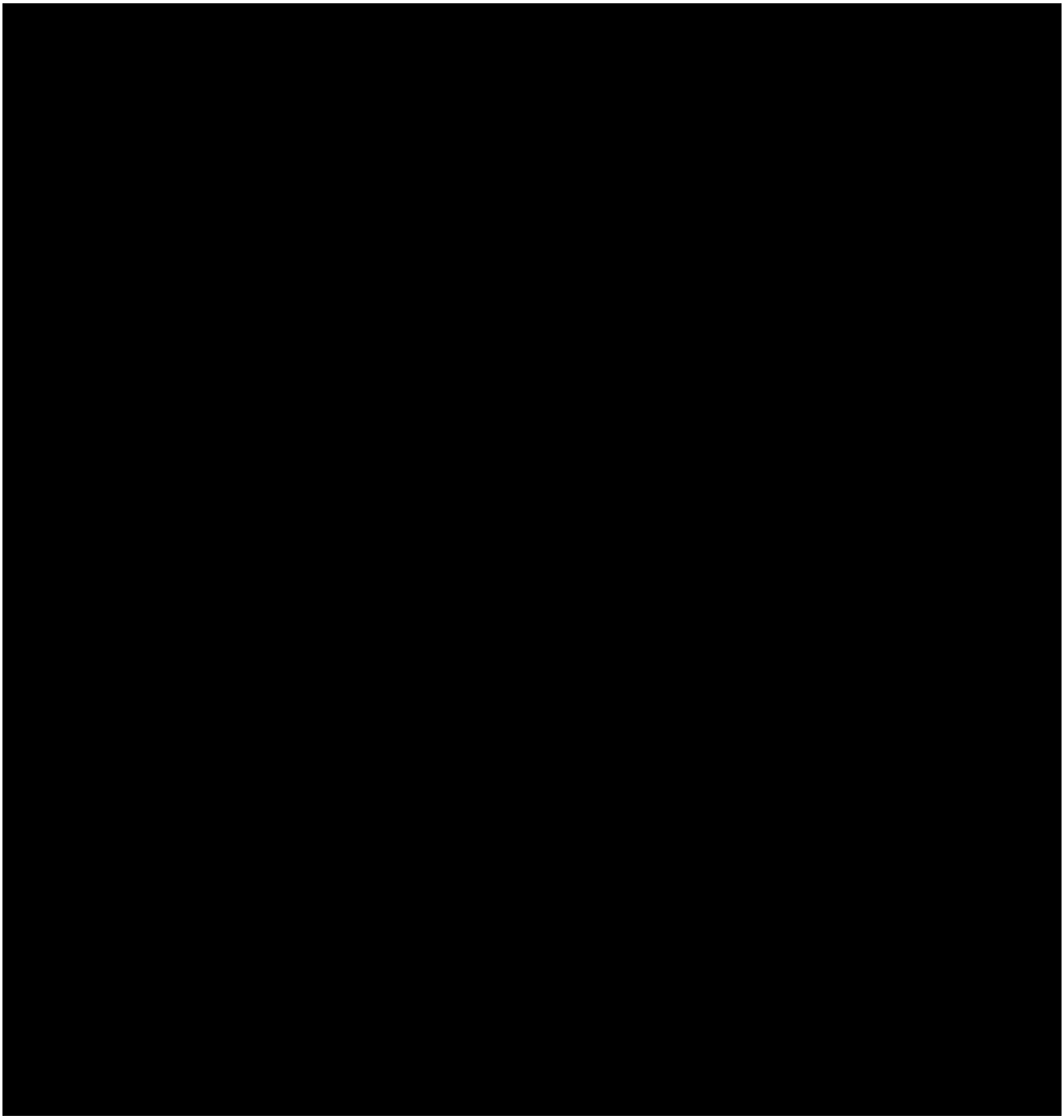
The frequency of occurrence of major bleeding (for Group B only) intraoperatively and up to 24 hours post-surgery will be summarized descriptively. The 95% Clopper-Pearson confidence interval will be calculated for the frequency.

Minimum unbound sum dabigatran concentrations at any time point since the end of first infusion up to 4 hours after the completion of the last infusion ($C_{min,1}$) will be summarized for all evaluable patients descriptively. A maximum 30 minutes delay in sample collection will

be allowed to include the result in the analysis.

Maximum reversal of anticoagulation as measured by aPTT and TT, at any time point since the end of first infusion up to 4 hours after the completion of the last infusion will be summarized similarly as the primary endpoint. Only central biomarker testing result will be used for this endpoint. Local assessment of aPTT will be explored as further endpoint. A maximum 30 minutes delay in sample collection will be allowed to include the result in the analysis.

Safety endpoints will be summarized descriptively. The details of AE handling is stated in section 7.8. Standard AE tables will be created for both on-treatment period and the entire study period. Special safety tables and listings (e.g. outcome event tables) will be created for the entire study period only, unless specified otherwise. Patients with thrombotic events will be summarized descriptively.



7.7 EXTENT OF EXPOSURE

Two 2.5g vials of idarucizumab will be administered no more than 15 minutes apart. The exposure will be summarized by the number and proportion of patients received one, two or partial vials of idarucizumab. In addition, the duration of infusion of each vial, the time between start of the first vial and end of the second vial will be descriptively summarized.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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 number 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). AEs occurrences, i.e. AEs entries on the eCRF (electronic case report form), will be collapsed into AEs episodes provided that all of the following applies:

- the same lowest level term was reported for the occurrences;
- the occurrences were time-overlapping or time-adjacent (time-adjacency of second occurrences is given if the second occurrence started at the end date if 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.

The analysis of adverse events will be based on the concept of treatment emergent adverse events. All adverse events occurring before the administration of first vial idarucizumab will be assigned to 'screening'. All AEs recorded after first vial of idarucizumab and until 5 days after the last dose of idarucizumab will be assigned to the on-treatment period. AEs with onset date after the on-treatment period will be assigned to post-treatment period. In addition, AEs with onset date before start of the trial treatment but with worsening in intensity during the treatment will also be assigned to the on-treatment period.

All AEs in the on-treatment period and the entire study period will be tabulated in total and according to seriousness, severity and possible relationship to trial medication. AEs in the entire study period will be listed.

According to ICH E3 (5), AEs classified as 'other significant' will include those non-serious and non-significant AEs with
(i) 'action taken = discontinuation' or 'action taken = reduced', or

(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Report Planning Meeting.

An overall summary of adverse events will be presented.

Frequency of patients with adverse events will be summarised by type of patient (group A, group B), primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3, for patients with serious adverse events, protocol-specified adverse events of special interest (AESI) as well as for patients with drug related AEs. The system organ classes will be sorted according to the standard sort order specified by EMA (European Medicines Agency). Preferred terms will be sorted by frequency (within system organ class).

In addition, frequency of subjects with AESI and non-serious adverse events that exceed 5%-threshold will be summarised by primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). Descriptive statistics will be calculated over time and for the difference from baseline including post examination values. Baseline is understood as the last available measurement before the first administration of idarucizumab.

Frequency tables of changes with respect to the reference range between baseline and last value on treatment will also be presented.

7.8.3 Vital signs

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

7.8.4 ECG

No ECG data will be collected or analysed. Any clinically significant new abnormal findings in ECG after the first screening ECG will be reported as adverse events and summarized descriptively.

7.8.5 Others

Outcome events (pulmonary embolism, deep vein thrombosis, transient ischemic attack, myocardial infarction, systemic embolism, hemorrhagic stroke, ischemic stroke, other stroke, bleeding, death) are identified using narrow SMQs (20000081 “embolic and thrombotic

events", 20000047 "myocardial infarction") and MedDRA preferred terms. Frequency of events will be summarized descriptively for Group A and Group B.

8. REFERENCES

1	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
2	*001-MCS-36-472:* "Standards and processes for analyses performed within Clincal Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.
4	*001-MCG-156*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", 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
6	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.

10. HISTORY TABLE

Table 10: 1 History table

Version	**Date (DD-Mmm-YY)**	**Author**	**Sections changed**	**Brief description of change**
Initial	**15-Dec-17**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct.
Final	**08-Jul-19**	[redacted]	None	This is the final TSAP without any modification.