Trial Statistical Analysis Plan

c16578188-04

BI Trial No.:	1321.6
Title:	Open label Phase I trial in healthy Chinese male and female volunteers to investigate pharmacokinetics and pharmacodynamics of idarucizumab to reverse dabigatran anticoagulant activity. Including Protocol Amendment 1 [c02286986-03]
Investigational Product(s):	Idarucizumab
Responsible trial statistician(s):	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	14 SEP 2017 SIGNED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis data set
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
BI	Boehringer Ingelheim
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DE	Dabigatran etexilate
dTT	Diluted thrombin time
ECG	Electrocardiogram
[redacted]	[redacted]
ETP	Endogenouos Thrombin Potential
HR	Heart rate
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
O*C	Oracle Clinical
PD	Pharmacodynamics
PDS	Pharmacodynamic set
PK	Pharmacokinetics
PKS	Pharmacokinetic set
PR	Pulse rate
PV	Protocol violation
QT	Time between the start of the Q-wave and the end of the T-wave in an ECG
QT(c)	QT interval, any correction
QTcB	QT interval, corrected according to Bazett's formula
QTcF	QT interval, corrected according to Fridericia's formula
SD	Standard deviation
[redacted]	[redacted]

Term	Definition / description
TSAP	Trial statistical analysis plan
WHO-DDE	World Health Organization Drug Dictionary Enhanced/Herbal

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 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

There has been no change in planned analyses from the statistical methods described in the CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoints will be used as defined in the CTP, Section 5.1.1.

5.2 SECONDARY ENDPOINTS

The secondary endpoints will be used as defined in the CTP, Section 5.1.2.

[redacted]

5.4 OTHER VARIABLES

5.4.1 Demographic data and baseline characteristics

- Sex (Male, female)
- Age [years]
- Height [cm]
- Body weight [kg]
- Body mass index [kg/m^2]
- Smoking status (Never smoked, Ex-smoker, Currently smokes)
- Alcohol status (Non-drinker, Drinks – no interference, Drinks - possibly interference)
- Medical history/baseline conditions
- Concomitant therapy

5.4.2 Safety data

The data used for safety assessment are specified in the CTP, Section 5.3.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

The treatment regimens/study intervals with short label, sort order and start date/time included in the treatment set-up in Oracle Clinical (O*C) are described in the analysis data set (ADS) plan. Codes, decodes and sort order for treatment regimen included in the treatment set-up in O*C are described in the ADS plan. Detailed specifications are described in the ADS plan.

For safety analyses, the treatment assignment will be applied as defined in the CTP, Section 7.3.4. The data recorded prior to first intake of dabigatran will be assigned to 'screening', and those between first intake of dabigatran until first idarucizumab intake will be assigned to ‘dabigatran period’, and those between first intake of idarucizumab until the EOT visit will be assigned to ‘dabigatran + treatment’, and those between EOT visit until the end of trial (FU2 visit) will be assigned to ‘post- treatment’, and those after the end of trial visit examination will be assigned to ‘post-study’.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The Table 6.2: 1 shows a list of all important protocol violations (PVs) since they may potentially affect the rights or safety of subjects. PVs are summarised into the following categories. They will be determined for entered subjects only. Exclusion of patients from analyses due to the PVs will be discussed at the final report planning meeting/the database lock meeting.

Table 6.2: 1 Important PVs

Category/ Code		Description	Example/Comment	Excluded from	Program/Manual
A		**Entrance criteria not met**			
	A1	Inclusion criteria not met			
	A1.1	age<18 or age>45 years	IN1 not met.	None	Program + Manual
	A1.2	Heathy volunteer criteria not met	IN2 not met.	None	Program + Manual
	A1.3	Weight <50 kg or (BMI<19.0 or BMI ≥24.0 kg/m^2)	IN3 not met.	None	Program + Manual
	A2	Exclusion criteria violated	Exclusion criteria not met as specified in the protocol.	None	Program + Manual
B		**Informed consent**			
	B1	Informed consent not available/not done	IN4 not met.	All	Program + Manual
	B2	Informed consent too late	Informed consent date was after Visit 1 date.	None	Program + Manual
C		**Trial medication and randomisation**			
	C1	Incorrect trial medication taken	Wrong medication	None	Manual
D		**Concomitant medication**			
	D1	Prohibited medication use	Prohibited medication	None	Manual

6.3 PATIENT SETS ANALYSED

All analyses will be based on the treated set.

- Treated set (TS):
  This subject set includes all subjects who received the idarucizumab.

- Pharmacokinetic set (PKS):
  This subject set includes all subjects who received the idarucizumab and who had at least one PK parameter.

- Pharmacodynamic set (PDS):
  This subject set includes all subjects in the TS who provide at least one evaluable predose and/or one on-treatment PD observation after the start of administration of dabigatran. This analysis set is used for all PD analyses.

6.4 SUBGROUPS

No subgroup analysis is planned.

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Safety data

With respect to safety, it is not planned to impute any missing values except for missing dates.

Missing or incomplete adverse event (AE) dates will be imputed according to Boehringer Ingelheim (BI) standards "Handling of missing and incomplete AE dates" (001-MCG-156_RD-01[1]).

6.6.2 Pharmacokinetic data

Missing data and outliers of PK data are handled according to "Noncompartmental Pharmacokinetic Analyses of Clinical Studies" (001-MCS-36-472_RD-01 [2]).

6.6.3 Pharmacodynamic data

Missing data and outliers of PD data are handled as PK according to "Noncompartmental Pharmacokinetic Analyses of Clinical Studies" (001-MCS-36-472_RD-01 [2]).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For safety evaluation (except for ECG), the baseline will be defined as the last available measurement prior to the first dabigatran administration.

For PD parameters of individual subject, the baseline (E_{base}) is defined as the arithmetic mean values at Day -1and Day 1 [0:00]. The E_{base} will be used for individual calculation of the ratio of PD parameters [PD value at each timepoint/E_{base}].

For all parameters [redacted], dTT and [redacted]), reversal to baseline is defined as a coagulation test value being below the upper limit normal (ULN) as determined based on the pre-dose values of the coagulation parameter prior to dabigatran drug administration in this study. In addition, reversal to baseline will be calculated using the ULN as determined based on the pre-dose values in studies of 1321.1and 1321.2 (Table 6.7: 1) as sensitivity analysis.

Table 6.7: 1 Upper limit normal values for PD parameters

	[redacted]	dTT [s]	[redacted]	[redacted]
ULN	[redacted]	35.5	[redacted]	[redacted]

7. PLANNED ANALYSIS

For End-Of-Text tables for non-PK parameters, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

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 subjects in the respective subject 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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the clinical trial report (CTR). Demographic variables are described in Section 5.4.1.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the CTR. Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary Enhanced/Herbal (WHO-DDE).

7.3 TREATMENT COMPLIANCE

Idarucizumab will be administered and monitored by the investigator, [redacted] deputy or members of [redacted] staff. The measured plasma concentrations of Idarucizumab will provide information regarding compliance. It is not intended to list the compliance separately.

7.4 PRIMARY ENDPOINT

The analysis of PK parameters is performed according to “Noncompartmental Pharmacokinetic Analyses of Clinical Studies” (001-MCS-36-472_RD-01 [2]).

Comparative figure of PD parameter of dTT (dTT: $AUEC_{above,\ 2\text{-}12}$ on day 4 without Idarucizumab and day 11 with Idarucizumab) will be presented in the presence or absence of Idarucizumab.

The following analyses will be performed:

- Percent (%) of subjects with dTT values (at least one value) reversed to baseline within time frame [completion of first infusion of Idarucizumab, completion of second infusion of Idarucizumb].
- Percent (%) of subjects with dTT values (all values) reversed to baseline for 2, 4, 6, 12 or 72 hours after completion of first infusion of Idarucizumab.

$AUEC_{2\text{-}12}$ of individual subject will be calculated from dTT ratio. $AUEC_{above,\ 2\text{-}12}$ based on dTT ratio will be calculated by subtracting the area under the 1 between 2 and 12 hour (1x

10[hrs]) after administration of Dabigatran from $AUEC_{2\text{-}12}$ based on dTT ratio (see also, "Noncompartmental Pharmacokinetic Analyses of Clinical Studies" (001-MCS-36-472_RD-01 [2])).

The percent (%) reduction in dTT of $AUEC_{above,\ 2\text{-}12}$ based on dTT ratio from day 11 compared to day 4 will be explored.

7.5 SECONDARY ENDPOINTS

The analysis of PK parameters for secondary endpoints is performed according to "Noncompartmental Pharmacokinetic Analyses of Clinical Studies" (001-MCS-36-472_RD-01 [2]).

[redacted]

7.7 EXTENT OF EXPOSURE

Frequency and percentage of patients will be summarized by Idarucizumab doses used.

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. All analyses of AEs will be based on BI standards as described in the BI guideline "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries (001-MCG-156 [3]).

All reported AEs for enrolled subjects will be coded with the most recent version of the MedDRA.

For analysis of AE, occurrence data on CRF will be collapsed into one AE as described in the AE guideline. Please refer (1) (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. The assignment of treatment regimen will be based on those defined in the CTP, Section 7.3.4.

Protocol specified adverse events of special interest (AESI) will be used as defined in the CTP, Section 5.3.6.1

According to ICH E3 (4), 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 AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for subjects with drug related AEs, for subjects with serious AEs, for subjects with drug related serious AEs, for subjects with AESI and for subjects with other significant AEs according to ICH E3 (4).

The system organ classes will be sorted according to the standard sort order specified by European Medicines Agency, preferred terms will be sorted by frequency (within system organ class).

Subjects with serious AEs, AESI or other significant AEs will be listed in Section 15.4.2 of the CTR.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5). Descriptive statistics will be calculated for original and normalized (if applicable) values over the time and for the difference from baseline including post examination values. Changes from baseline to last value on treatment in categorization with

respect to the reference range will also be presented by frequency tables.

Anti-drug antibodies (ADA)

The analysis of anti-idarucizumab antibodies will be presented in Section 15.8 of the CTR. Only descriptive statistics are planned for this section of the report based on the treated set.

7.8.3 Vital signs

Only descriptive statistics of vital signs (blood pressure, PR, and body temperature) over the time (original value and change from baseline) are planned for this section of the CTR.

7.8.4 ECG

No ECG data are collected in this study.

7.8.5 Others

A frequency table will be provided for local tolerability.

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_RD-01*: "Noncompartmental Pharmacokinetic Analyses of Clinical Studies", current version; IDEA for CON.

3 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", version 5; IDEA for CON.

4 *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.

5 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

9. ADDITIONAL SECTIONS

Not applicable as no additional information is needed.

10. HISTORY TABLE

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

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Initial	30-Mar-17	[redacted]	None	This is the initial TSAP without any change.
Initial	06-Apr-17		None	No change in the content, but redo the process due to some error in system process.
Final	17-Aug-17		Sections 5, 6 & 7	This is the final TSAP. Some revisions are made upon the initial TSAP in sections 5, 6 and 7.
Revised	14-Sep-17		Section 6.7 & 7.4	Revise the calculation rules for reversal to baseline in section 6.7. Minor change in section 7.4 from “within 2, 4, 6, 12” to “for 2, 4, 6, 12” to be consistent in wording with other studies.