TRIAL STATISTICAL ANALYSIS PLAN c15269647-02

BI Trial No.:	1321.15
Title:	The drug use-results survey (All-Case Surveillance) on Prizbind® for Intravenous Solution 2.5 g in Japan
Investigational Product(s):	Idarucizumab
Responsible trial statistician(s):	[redacted] [redacted] Address: [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	19 MAR 2021 REVISED
Version:	"Revised"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse Drug Reaction
ADS	Analysis data set
AE	Adverse Event
aPTT	activated Partial Thromboplastin Time
BMI	Body Mass Index
CCr	Creatinine clearance
DBP	Diastolic Blood Pressure.
FFP	Fresh frozen plasma
GI	Gastrointestinal
ICH	Intracranial Hemorrhage
LLT	Lowest Level Term
MedDRA	Medical Dictionary For Regulatory Activities
NIS	Non-interventional Study
PCC	Prothrombin Complex Concentrate
PMS	Post Marketing Surveillance
PR	Pulse Rate
PT	Preferred Term
PV	Protocol Violation
Q1	Lower Quartile
Q3	Upper Quartile
RBC	Red Blood Cell
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
TIA	Transient Ischemic Attack
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal

3. INTRODUCTION

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 Non-interventional Study (NIS) protocol, including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS protocol Section 9.7 “DATA ANALYSIS”. Therefore, TSAP readers may consult the NIS protocol 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.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analysis from the statistical methods described in the NIS protocol.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for effectiveness, the primary objective of the PMS study is the evaluation of safety (see the NIS protocol Section 9.3.2.1).

5.2 SECONDARY ENDPOINT(S)

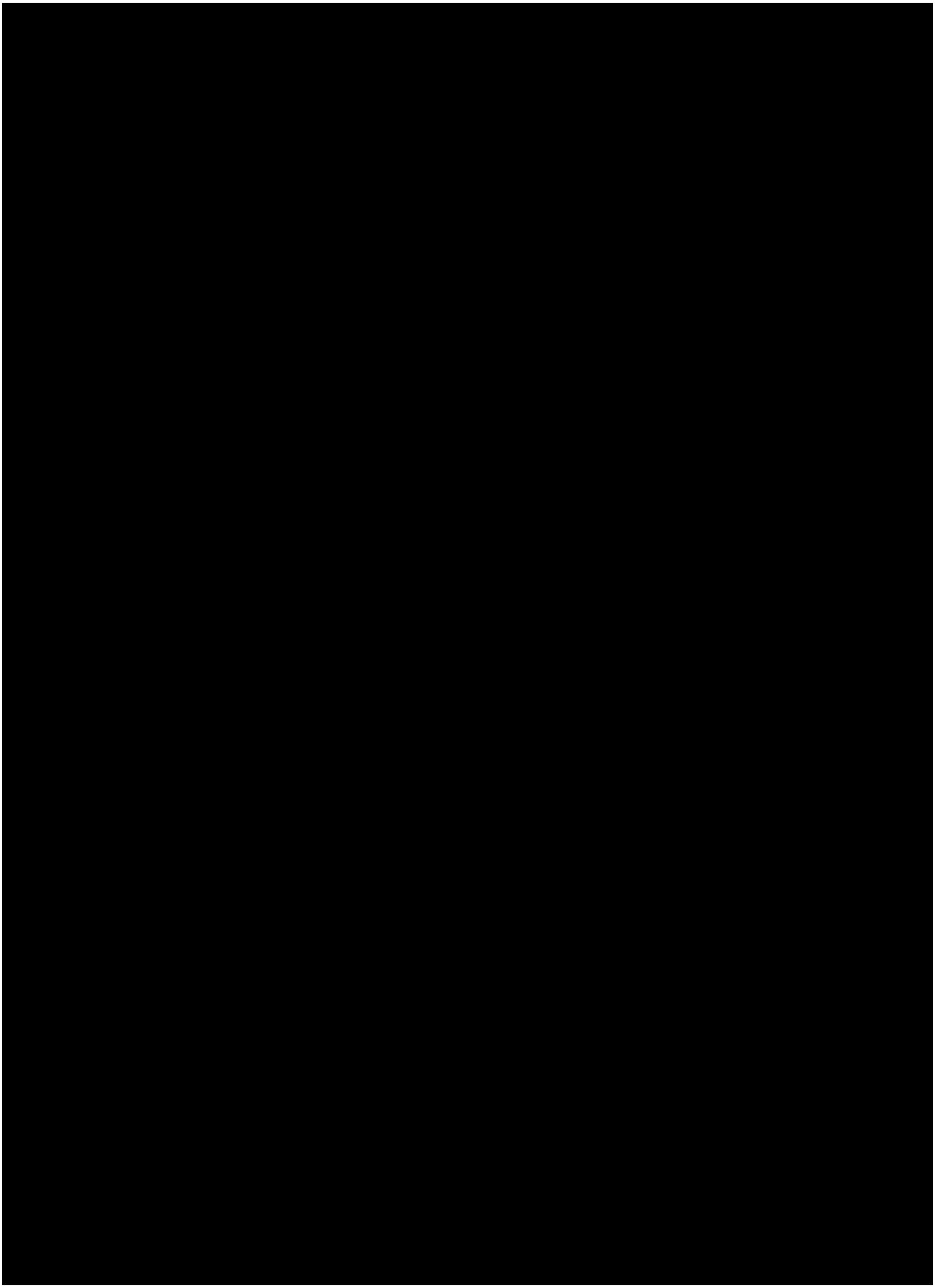
5.2.1 Key secondary endpoint(s)

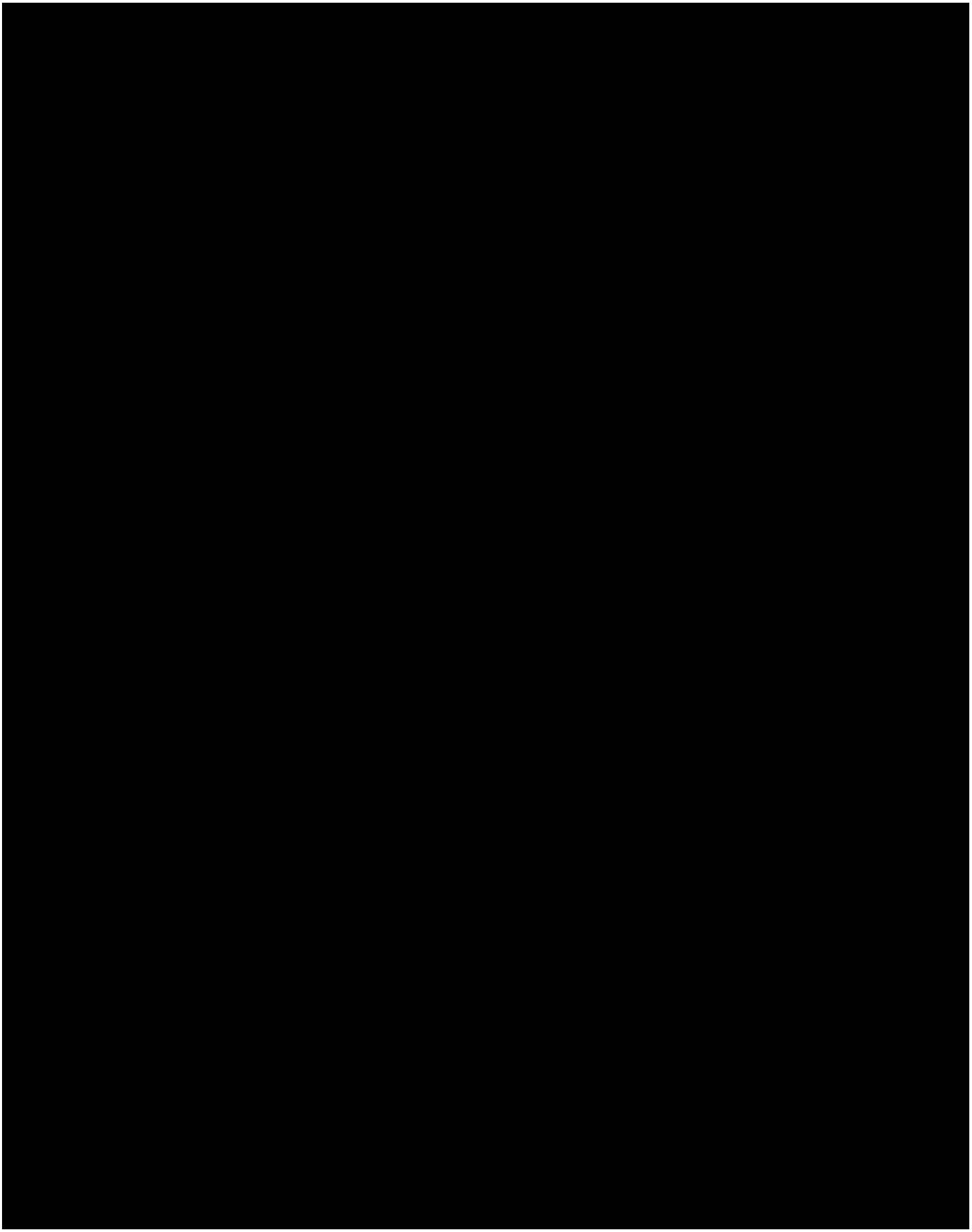
This section is not applicable as no key secondary endpoint has been specified in the protocol.

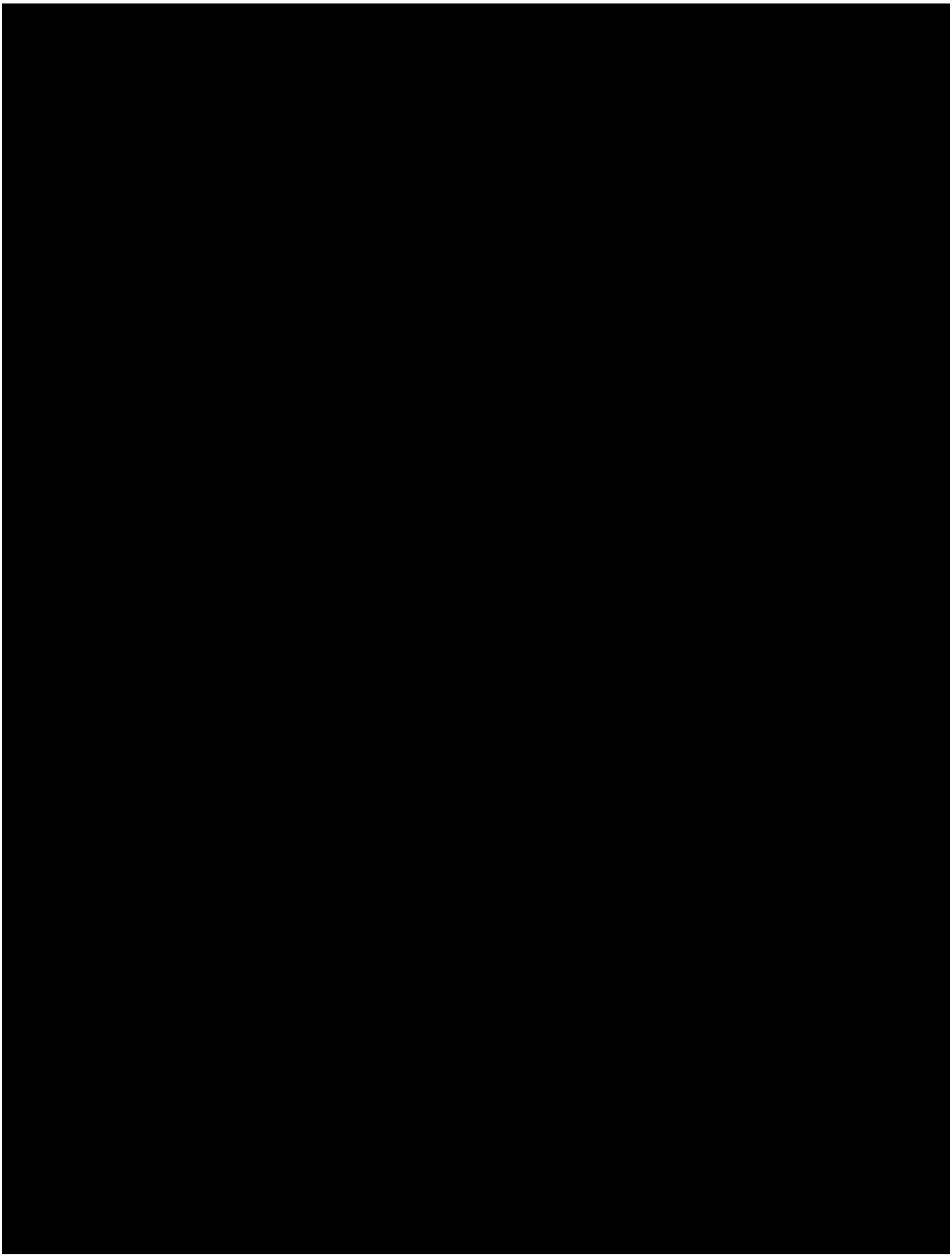
5.2.2 Secondary endpoint(s)

The secondary objective of the PMS study is following variable (refer to the NIS protocol Section 9.3.2.2).

- Reversal of anticoagulation as measured by coagulation tests (aPTT)
  The maximum effect on the anticoagulant activity within 4 hours after the completion of administration:
  Maximum Reversal: { (predose aPTT – minimum postdose aPTT) /
  (predose aPTT – ULN) } × 100%
  ULN: upper limit of normal in each site







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments, please refer to NIS protocol Section 9.1. The technical specification for treatment set-up is described in the analysis data set (ADS) plan. For effectiveness analyses, data up to 4 hours 30 minutes after last treatment intake will be considered as on treatment for aPTT. For safety analyses, data up to 5 days after last treatment intake will be considered as on treatment for AE.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The right-most column describes which PVs will be used to exclude patients from the different patient analysis sets. The final decision about which patients will be excluded from analysis sets will be taken during the course of the study and at report planning meetings before database lock at the latest.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Detection method	Excluded from
A		**Entrance criteria not met**			
	A1	Off-label use	Reason of use is “Other” only.	Automated	Effectiveness
	A2	No treatment with Prazaxa		Automated	Effectiveness
B		**Trial medication**			
	B1	No treatment with Prizbind		Automated	Safety
C		**Missing data**			
	C1	No all effectiveness data	There is none of following effectiveness data:a pair of predose/postdose aPTT, date/time of hemostasis, bleeding category and information about re-start anticoagulant therapy	Automated	Effectiveness
D		**Trial specific**			
	D1	Duplicated registration	In different patient number, sex, birthday, start date of first administration of Prizbind, height, weight and site name are the same.	Manual	Safety
	D2	Registration rule not followed	See the NIS protocol Section 9.2.2.2 and 9.2.2.3	Manual	Safety
	D3	Site contract is not valid		Manual	Safety

6.3 SUBJECT SETS ANALYSED

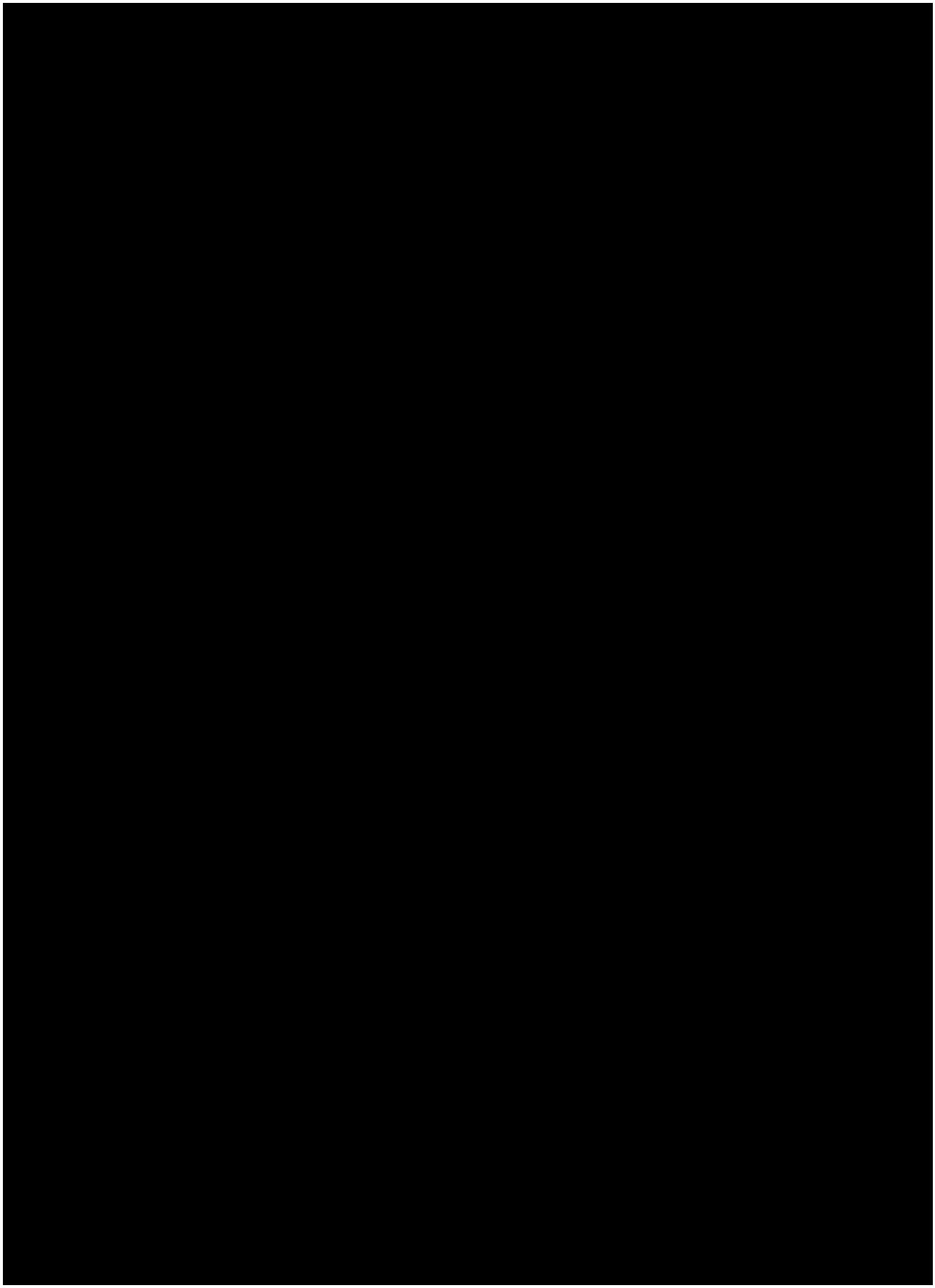
The safety set will be the basis of all demographic, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

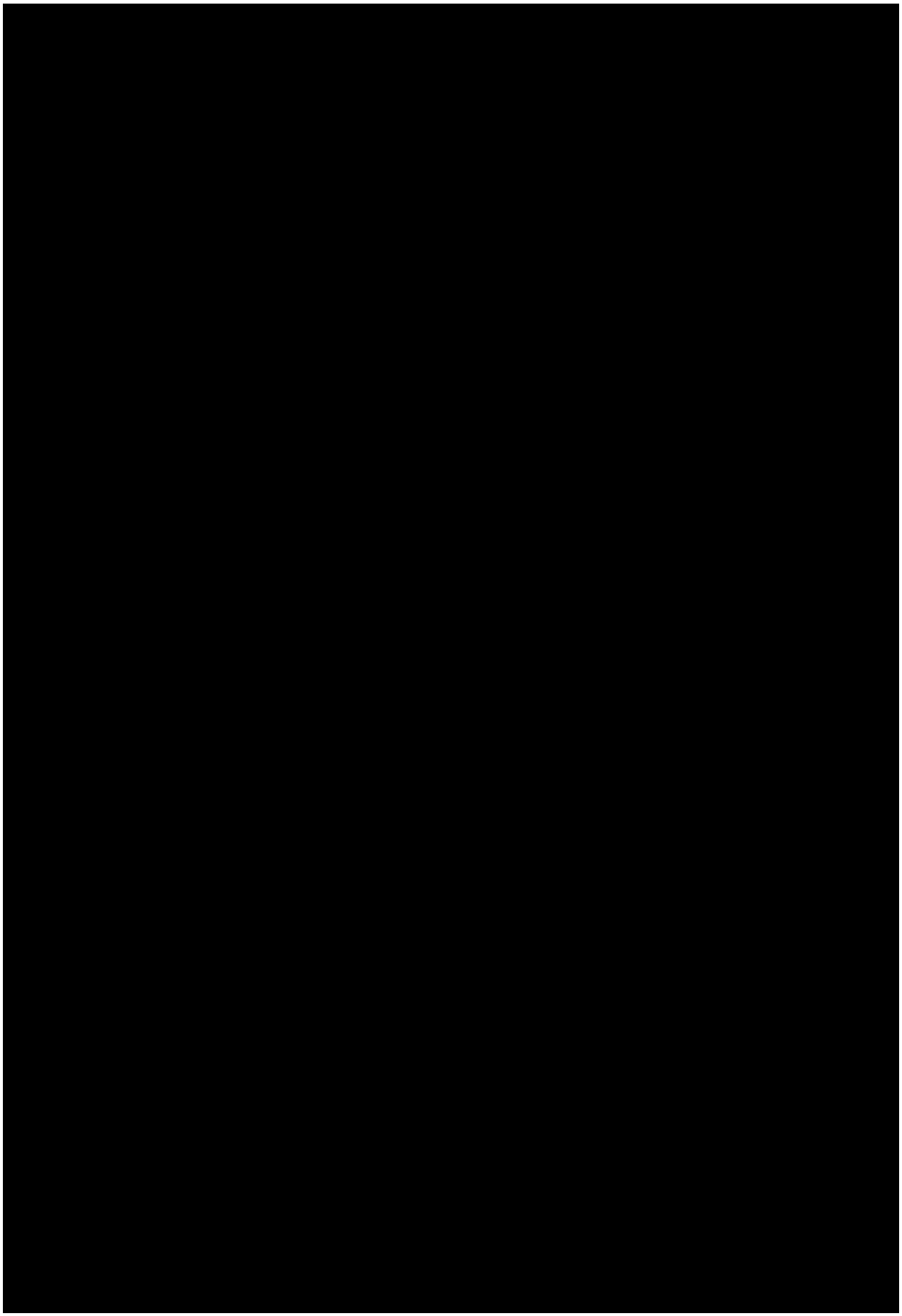
- Safety set:
  This patient set includes all patients who had no invalid registration, who were documented to have taken at least one dose of Prizbind.

- Effectiveness set:
  This patient set includes all patients with Prizbind in the safety set who have at least one available effectiveness data.

Table 6.3: 1 Subject sets analyzed

Class of endpoint	Subject set								
	Safety set					Effectiveness set			
	All	Group A	Group B	Group A+B	Other	All	Group A	Group B	Group A+B
Primary endpoints	X								
Secondary endpoint						X			
[redacted]									
Disposition	X								
Demographic and baseline characteristics Medical history/concomitant diseases Concomitant medication Concomitant therapies Baseline coagulation test Treatment exposure Termination of PMS	X								
Bleeding assessment		X		X					
Surgery / invasive procedure assessment			X	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 or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (1).

For missing of the end date of follow up period, the last date of all dates in CRF is imputed. If the end date of follow up period is entered, but earlier than the last date of all dates in CRF, the end date of follow up period is replaced by the last date of all dates in CRF.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to effectiveness and safety endpoints, the term "baseline" or "predose" refers to the last observed measurement prior to administration of Prizbind.

In this analysis, 1st day is defined as first starting day of administration for Prizbind.

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

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 two decimal places. The category missing will be displayed only if there are actually missing values.

Tables will be displayed by purpose of use (Group A, Group B, Group A+B, Other and All) categorized by trial team.

In addition, individual values on demographics, safety and effectiveness will be presented in subject data listings.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Frequency of patients with concomitant diseases will be summarized by system organ class (SOC) and preferred term (PT).
Concomitant diseases: Diseases that are suffering from at the first administration of Prizbind.
Concomitant medication will be coded by latest version of ‘Nihon-iyakuhinshu’.

7.3 TREATMENT COMPLIANCE

Compliance data is not collected in this study.

7.4 PRIMARY ENDPOINT(S)

The analysis of the primary endpoint is described in Section 7.8.1.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

The analysis for secondary endpoints will be performed for patients (aPTT at baseline >ULN) on the effectiveness set, as defined in the NIS protocol Section 9.3.2.2. N / Min / Q1 / Median / Q3 / Max will be displayed. If calculated reversal is > 100, it will be set to 100. The values will be capped at 100%.

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety set.

7.8.1 Adverse events

Unless otherwise specified, the analyses of adverse events (AEs) will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs. In the tabulation of ADRs, serious ADRs, important identified risks and important potential risks by SOC and PT, not only the number of patients but also number of events will be dislayed. AEs with onset date prior to treatment of Prizbind which lead to death after Prizbind administration are not included in AE analysis but will be used when calculating time to death using Kaplan Meier survival estimates.

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, 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).
All adverse events occurring after the residual effect period will be assigned to ‘post-treatment. The frequency and percentages of ADRs, AEs, serious adverse events (SAEs), important identified risks and important potential risks occurred in treatment + post-treatment period as well as treatment period will be tabulated. For details on the treatment definition, see Section 6.1. Also, ADRs and SAEs up to 28 days after last treatment intake (=observation period) will be tabulated.
An overall summary of AEs will be presented.

The frequency of patients with ADRs will be tabulated by Prizbind dose at onset, SOC and PT according to the most recent MedDRA version.
Separate tables will be provided for patients with SAEs, serious ADRs and for patients with each of the following AEs for important identified risks: hypersensitivity (shock and anaphylaxis) and important potential risks: immunogenicity, thrombotic event (ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism). Important identified risks and important potential risks are defined in accordance with the Japanese RMP. The details of these risks are defined in the external file

'MedDRA_verxxx.xlsx (current ver.)'. The file is stored in BIRDS 'Section 8 TSAP and programming'.
For AEs leading to discontinuation of Prizbind, a summary table will also be created based on patients who discontinued the treatment due to AEs.

In addition, summaries for the time to onset of first episode for the ADRs will be tabulated by duration, by primary SOC, and PT.
An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Prizbind as "Yes". The SOCs will be sorted according to the standard sort order specified by European medicines agency, PTs will be sorted by frequency (within SOC).

A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness as "Serious".

Mortality rate at the end of follow-up period will be calculated descriptively by KM estimate. It will be also stratified by ICH, upper or lower GI bleeds on-going at baseline assessment and other for Group A and Group A+B categorized by trial team.

To compare risks of overall ADR, SAE, serious ADR as well as each of the important potential risks in different patient subgroups, frequency tabulation stratified by different patient subgroups will be provided with odds ratios and exact 95% confidence intervals whenever specified (see Section 6.4).

7.8.2 Laboratory data

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.3 Vital signs

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.4 ECG

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.5 Others

No other analysis is planned.

8. REFERENCES

[redacted]

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
Final	**17-Apr-2019**	[redacted]	None	This is the final TSAP without any modification
Revised	**19-Mar-2021**	[redacted]	2	Abbreviations not used in TSAP are removed.
			[redacted]	[redacted]
			6.3	Table 6.3: 1 is rearranged due to addition of new group.
			[redacted]	[redacted] Modification in Section 5.4 is reflected.
			6.6	Imputation rules for time to re-start anticoagulant therapy are deleted.
			7.2	Description for definition of concomitant diseases is added.
			[redacted]	[redacted]
			7.8.1	Description for number of events is added. Analyses for important identified risks and important potential risks occurred in treatment + post-treatment period are added. Description for definition of important identified risks and important potential risks is added.
			8	Reference sources are modified.