Boehringer Ingelheim

NON-INTERVENTIONAL STUDY PROTOCOL

Document Number:	**c10292519-03**
BI Study Number:	1321.15
BI Investigational Product(s):	Idarucizumab
Title:	The drug use-results survey (All-Case Surveillance) on Prizbind® for Intravenous Solution 2.5 g in Japan
Brief lay title	All-Case surveillance of Prizbind®
Protocol version identifier:	3.0
Date of last version of protocol:	25 March 2019
PASS:	Yes
EU PAS register number:	EUPAS15981
Active substance:	Idarucizumab (V03AB37)
Medicinal product:	Prizbind® for Intravenous Solution 2.5 g
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	To evaluate safety and effectiveness of Prizbind® for Intravenous Solution 2.5 g under Japanese clinical condition
Country(-ies) of study:	Japan
Author:	[redacted] Phone: [redacted] Fax: [redacted] [redacted]

	[redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	The signature of EU-QPPV is provided electronically
Date:	25 March 2019

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
CRF	Case Report Form
CTP	Clinical Trial Protocol
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-QPPV	European Union-Qualified Person for Pharmacovigilance
GPSP	Good Post-marketing Study Practice
J-RMP	Japanese Risk Management Plan
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
PSUR	Periodic Safety Update Report
SAE	Serious Adverse Event
TSAP	Trial Statistical Analysis Plan

3. RESPONSIBLE PARTIES

Marketing authorization

[redacted]

Study Site Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the drug use-results survey tracking system which manages the contracts with site and investigators name.

Biostatistics

Trial Statistician (TSTAT) assigned to 1321.15 is responsible for overall biostatistics.

Programming

Trial statistical programmer (TPROG) assigned to 1321.15 is responsible for overall SAS statistical programming.

Data Management

Trial Data Manager (TDM) assigned to 1321.15 is responsible for overall data management

Medical adviser

[redacted]

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prizbind® for Intravenous Solution 2.5 g			
Name of active ingredient: Idarucizumab (V03AB37)			
Protocol date: 23 Sep 2016	**Study number:** 1321.15	**Version/Revision:** 3.0	**Version/Revision date:** 25 Mar 2019
Title of study:	The drug use-results survey (All-Case Surveillance) on Prizbind® for Intravenous Solution 2.5 g in Japan		
Rationale and background:	The Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices requires accumulating safety and effectiveness data of launched products in Japan for re-examination. Since there are a limited number of Japanese subjects treated in clinical trial, All-Case Surveillance is planned to collect safety and effectiveness data of Prizbind® for Intravenous Solution 2.5 g. The PMS plan is a part of the local Risk Management Plan in Japan (J-RMP). The J-RMP was submitted to the Japanese regulatory authority, the PMDA as a part of J-CTD and need to be approved by PMDA as approval condition. After 8years from approval, the results of the PMS are needed to be submitted to the PMDA, as a part of the re-examination dossier.		
Research question and objectives:	This PMS is designed to investigate the safety and effectiveness of Prizbind® for Intravenous Solution 2.5 g in patients under Japanese clinical condition according to the Japanese package insert.		
Study design:	Non-interventional study based on newly collected data. All patients administrated Prizbind® for Intravenous Solution 2.5 g after the approval at the sites contracted with the sponsor will be registered. This study permits the contract with the sites both before and after patient's administration of Prizbind® to collect the data retrospectively. The study will consist of data from baseline visit to 4weeks follow-up for patients who initiate Prizbind® for Intravenous Solution 2.5 g. The patient registration should continue until the approval condition will be removed. CRF will not be collected after the number of cases reaches target number.		
Population:	Inclusion criteria - Patients who are prescribed with Prizbind® for Intravenous Solution 2.5 g by the discretion of investigators Exclusion criteria - None		

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Prizbind® for Intravenous Solution 2.5 g			
Name of active ingredient: Idarucizumab (V03AB37)			
Protocol date: 23 Sep 2016	**Study number:** 1321.15	**Version/Revision:** 3.0	**Version/Revision date:** 25 Mar 2019
Variables:	Primary outcomes Any suspected ADRs (primary outcome), Serious AEs, and AEs for important potential risks(hypersensitivity, thrombotic event) Secondary outcomes Effectiveness will be assessed with a focus on the following variable as secondary outcome. Reversal of anticoagulation as measured by coagulation test (aPTT, activated partial thromboplastin time)(secondary outcome) [redacted]		
Data sources:	Case Report Forms (CRFs) for individual patients will be provided by the sponsor. After the medical examination and observation at the specified points (Baseline, up to Week 4, or discontinuation) are completed, the investigator needs to immediately enter data of the registered patients (including withdrawals and dropouts) in CRF. In case that any adverse events occur, the data should be as soon as possible entered into CRF.		
Study size:	300		
Data analysis:	Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study. Analyses are descriptive in nature including means, standard deviation, min, Q1, medians, Q3, max, frequency and percentages.		
Milestones:	Start of data collection: 28 September 2016 End of data collection: March 2020 (in plan) Final report of study results: 4Q 2020 (in plan)		

Table 1 Flow chart

Observation / Evaluation time points are approximate. Collected data should be reported as those to the closest available time.

Item \ Time	Observation period			
	Baseline before treatment	Drug administration	48 hours after administration	4weeks/or discontinuation
Patient registration*[1]	X			
Patient demographics	X			
Medical history	X			
Dabigatran use	X			
Bleed assessment Surgery/Procedure	X (to be reported throughout the observation period)			
Prizbind® administration		X		
Coagulation tests*[2]	X (to be reported throughout the period)			
Concomitant medications /therapy	X (to be reported throughout the observation period)			
Blood pressure, pulse rate	(X)(to be reported throughout the period)			(X)(to be reported)
Laboratory tests	(X) (to be reported throughout the period)			(X)(to be reported)
Adverse events		X (to be reported throughout the period)		
Re-start anticoagulant therapy				X

*1: Patients administered Prizbind® for Intravenous Solution 2.5 g after approval will be registered regardless of date of contract for this study.

*2: All aPTT values monitored during the observation period should be entered.
(X): If applicable

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	6 Jun 2018	9.3.3	Amendment	In order to harmonize the CTP and the CRF
3.0	12 Mar 2019	9.1, 11.2	Update	In order to transfer to the only-enrollment phase

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	28 September 2016
End of data collection	March 2020 (in plan)
Registration in the EU PASS register	Registered
Final report of study results	4Q 2020 (in plan)

7. RATIONALE AND BACKGROUND

The reversal of the anticoagulant effects of dabigatran by idarucizumab, a humanised monoclonal antibody fragment, has been demonstrated in volunteers (studies 1321.1, 1321.2 and 1321.5) and patients from the Study 1321.3(about 500 patients were enrolled in Q2 2016).

[redacted]participated in Global phase III study (1321.3) after phase I study (1321.5) in Japanese subjects (60 cases)was finished. For the application for marketing approval in Japan, an interim analysis of 1321.3 was conducted by using data in 243 patients (including 4 Japanese patients) as of October 26, 2015. These clinical study results showed that idarucizumab was effective for neutralizing the anticoagulant effect of dabigatran and a favorable safety profile of idarucizumab.
On the other hand, a limited number of Japanese subjects were treated in clinical trials. MHLW may require All-Case Surveillance of idarucizumab as an approval condition. Therefore, [redacted]plans All-Case Surveillance to collect safety and efficacy data of idarucizumab (Prizbind® for Intravenous Solution 2.5 g) after its marketing launch in Japan.

Japanese regulation related to Post Marketing Surveillance (PMS)
This PMS is planned according to the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices. The law requires in principle that data on the safety and effectiveness of all launched products to be accumulated under Japanese clinical condition. The PMS is a part of the local Risk Management Plan in Japan (J-RMP) to be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the local regulatory agency in Japan at New Drug Application. After 8years from approval of registration, the data collected in the PMS are required to be submitted to PMDA according to the process of re-examination.

Japanese regulation related to All-Case Surveillance
The All-Case Surveillance means a use-results survey that is conducted to collect information on all patients who have used the product since its launch until a data from certain number of cases have been accumulated. The All-Case Surveillance is required for products that needs the background information of patients treated with the product as well as safety and effectiveness issues related to the product for reaffirming approval details and collecting information which is essential for proper use at the earliest possible stage, thoroughly.
For example, the regulatory agency may require the implementation of the All-Case Surveillance for a pharmaceutical product as an approval condition when there are only a small number, or even no cases existing in clinical trials in Japan and when there are any concerns about the pharmaceutical product regarding the occurrence of serious adverse drug reactions. Necessity for the All-Case Surveillance is determined by the following steps: review in PMDA, subsequent discussion by the Pharmaceutical Affairs and Food Sanitation Council, and the final decision by MHLW.

8. RESEARCH QUESTION AND OBJECTIVES

This PMS is designed to investigate the safety and effectiveness of Prizbind® for Intravenous Solution 2.5 g in patients under Japanese clinical condition according to the Japanese package insert.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on new data collection to gather data on safety and effectiveness of the Prizbind® for Intravenous Solution 2.5g under Japanese clinical condition. Patients who have been treated with dabigatran etexilate and required rapid reversal of the anticoagulant effects of dabigatran enter the study. Prizbind® is given intravenously, as idarucizumab at 5 g/dose (2 x 2.5 g/50 mL).

The study will consist of data from baseline visit to 4 weeks follow-up for patients who initiate Prizbind® for Intravenous Solution 2.5 g.

The study will be initiated after the approval of Prizbind® for Intravenous Solution 2.5 g in Japan. All patients administrated Prizbind® for Intravenous Solution 2.5 g after the approval at the sites contracted with the sponsor will be registered. The study permits the contract with the sites both before and after patient's administration of Prizbind to collect the data retrospectively. CRFs of 300 patients will be collected. However the patient registration continues until the approval condition has been removed.

Information will be collected via CRFs for patients who have been administered Prizbind up to and including 14 April 2019. For patients administered Prizbind after the time point, no pre-specified information will be collected via CRFs. Following the time point, patients will only be registered in order to count the number of patients being administered Prizbind at every site, for so long as it is required by PMDA.

The primary outcome of this study is the frequency of patients with any suspected adverse drug reactions (ADRs)

The secondary outcome of this study is reversal of anticoagulation as measured by aPTT

9.2 SETTING

9.2.1 Study sites

All sites that Prizbind® for Intravenous Solution 2.5 g administered to patients will participate in this study. The sites will be contracted with [redacted]
A medical representative (MR) will explain the objectives and design of this study to the investigators at study sites and exchange a written contract with the head of the study site (e.g., hospital director).The sites which do not exchange a contract beforehand will be requested, when MR provides Prizbind® material including documents for this study and the package insert etc.to the sites, to inform of patient who administered Prizbind® to [redacted]

9.2.2 Study population

9.2.2.1 Inclusion / exclusion criteria

Inclusion criteria

- Patients who are prescribed with Prizbind® for Intravenous Solution 2.5 g by the discretion of investigators

Exclusion criteria

- None

9.2.2.2 Registration period

From the 28 September 2016 until until the approval condition will be removed.

9.2.2.3 Patient registration method

At each study site, all patients who initiate treatment with Prizbind® for Intravenous Solution 2.5 g after the approval will be registered into this study.

Paper registration form will be used to collect necessary information and will be sent to the sponsor by fax.

End of registration

Patient registration will be stopped after the approval condition will be removed.
Only patient registration will be continued and CRF data will not be collected after the number of cases reaches target number.

9.2.3 Study visits

Collected data should be reported as those to the closest available time
(see Table 1).

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Emergence of any effectiveness/safety information that could significantly affect continuation of the study
2. Violation of Good Post-marketing Study Practice (GPSP), the NIS protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the second reason).

9.3 VARIABLES

9.3.1 Exposures

Dosage and administration: Prizbind® (2 x 2.5 g/50 mL) is administered intravenously, as two consecutive infusions over 5 to 10 minutes each or as a bolus injection in adults.

Exposure to Prizbind®: The total dose is 5 g (two 2.5g vials).

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Safety will be assessed with a focus on the following variables, frequencies and percentages.

- Any suspected ADRs (primary outcome)
- Serious AEs
- AEs for important potential risks*; hypersensitivity, thrombotic event (ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism) *: Immunogenicity will be assessed by clinical signs and symptoms of hypersensitivity.

How to assess and report AEs including the definitions are described in section 11.

9.3.2.2 Secondary outcomes

Effectiveness will be assessed with a focus on the following variable as secondary outcome.

- 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

[redacted]

[redacted]

9.3.3 Covariates

Baseline characteristics and observation items

After the medical The following items will be considered as the baseline characteristics. For all interventions/measures dates will be recorded. (see Table 1).

Demographics:
- Dabigatran Use(start date, daily dose, times/day, date and time of last intake)
- Prizbind® purpose of use(life-threatening or uncontrolled bleeding, emergency surgery/urgent procedures, other)
- Bleeding location, severity, start date and time, bleeding related to trauma
- Type of surgery/urgent procedure
- In/out patient
- Gender
- Age (birth year)
- Height
- Weight
- hypersensitive disposition
- Pregnancy
- Medical history/concomitant diseases
- History of bleeding events
- Department (emergency, cardiovascular, Neurosurgery, Neurology, Gastroenterolog, other)
- Participation of dabigatran clinical trial

Administration of Prizbind® :
- Treatment (dose/an injection, Start date and time, end date and time, consecutive infusions or as bolus injection)
- Primary reason of discontinuation for the survey

Bleeding / Surgery:
- Bleeding Status (Stopped, Reduced, No change, worsened, Temporarily stopped and re-bleeding,Not assessable, time and date)
- Volume of lost Blood (if applicable)
- Surgery/urgent procedures (indication, start date and time, end date and time)

Coagulation test values (if applicable):
aPTT, PT-INR, Fibrinogen, FDP, D-dimer
All aPTT values monitored during the observation period should be entered.

Concomitant medications:

- Treatment period (Start date, end date)
- Reason for use

Concomitant therapies (use of blood products)
- blood products/transfusion (Product, Number of Unit, Treatment period)
- FFP, packed RBCs, platelets, whole blood, volume expanders, tranexamic acid, cryoprecipitate, PCCs, Factor VIIa and any other hemostatic agents
- Dialysis(Yes/no)

Blood pressure, pulse rate:
- Systolic/ diastolic blood pressure, Pulse rate

Re-start anticoagulant therapy
- Re-Start date and time
- Name of medication, dose

Laboratory tests (if applicable):
- Liver function test (ALT, AST, Total Bilirubin, Alkaline Phosphatase (ALP))
- Renal function test (BUN, Creatinine)
- Na+, K+, Cl-
- Albumin
- Plasma glucose
- Creatine kinase (CK-MB:if increased)
- Triglyceride,Cholesterol (Total)
- Hematology(White blood Cell Count, Red blood Cell Count, Hemoglobin, Hematocrit, Platelet Count)

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor.

After the medical examination and observation at the specified points (Baseline, up to 4 weeks, or discontinuation) are completed, the investigator needs to immediately enter data of the registered patients (including withdrawals and dropouts) in CRF. In case that any adverse events occur, the data should be immediately entered into CRF.

9.5 STUDY SIZE

It is planned to collect 300 patients.

A sample size of 300 patients was planned in consideration of post-marketing occurrence of haemorrhagic events observed for Prazaxa® (based on the periodic safety update reports) and on the basis of feasibility.

Important potential risks (thrombosis and hypersensitivity) are considered as the key survey items. If real incidence rates of thrombosis and hypersensitivity in Japanese patients are same

as shown in the interim data in Study 1321.3 (5.3% and 12.3%) [c03666927-01], 95% confidence interval of their incidence rate is shown in the Table 2.

To ensure the same accuracy of the estimation (95% confidence interval: 2.8% to 9.0% (thrombosis), 8.4% -17.1% (hypersensitivity) in this study, about 250-300 cases is required with conservative estimation. Further, with a sample size of 300 patients, any ADR with frequency of 1% or higher can be detected with probability of 95% or greater in at least one patient.

Table 2 95% confidence interval of the incidence rate

N	Incidence rate	95% confidence interval		Upper-Lower
		Lower	Upper	
Thrombosis				
100	5.30%	1.7%	11.8%	10.1%
150	5.30%	2.2%	10.3%	8.1%
200	5.30%	2.6%	9.4%	6.8%
250	5.30%	2.9%	8.9%	6.0%
300	5.30%	3.0%	8.5%	5.5%
350	5.30%	3.2%	8.2%	5.0%
400	5.30%	3.3%	8.0%	4.7%
Hypersensitivity				
100	12.30%	6.5%	20.5%	13.9%
150	12.30%	7.5%	18.7%	11.2%
200	12.30%	8.1%	17.7%	9.6%
250	12.30%	8.5%	17.0%	8.6%
300	12.30%	8.8%	16.6%	7.8%
350	12.30%	9.0%	16.2%	7.2%
400	12.30%	9.2%	15.9%	6.7%

9.6 DATA MANAGEMENT

Data management is going to be outsourced to CRO(s). Detailed data management process with the CRO(s) will be described as data management procedure (or plan) which will be approved by BI-TDM and the CRO(s) before the initiation of DM operations. Data management and statistical software(s) are to be determined with the CRO(s) and described in the procedure (or plan).
Paper-based case report form is used for 1321.15 and monitoring is not applicable for PMS in Japan.

	Contract research organizations
Name	[redacted]

9.7 DATA ANALYSIS

This is a non-interventional study based on new data collection to gather data on safety and effectiveness of the Prizbind® for Intravenous Solution 2.5 under Japanese clinical condition. Analyses for safety, effectiveness and baseline characteristics are descriptive in nature including means, standard deviation, min, Q1, medians, Q3, max, frequency and percentages.

Per local regulation, any patient who meets at least one of the following criteria is treated as ineligible for all analyses:

- No follow-up visit data are available
- No required registration procedure is followed
- No valid site contract is available

9.7.1 Main analysis

All outcome events are based on reported AE data which will be handled according to BI standards (see the section below).

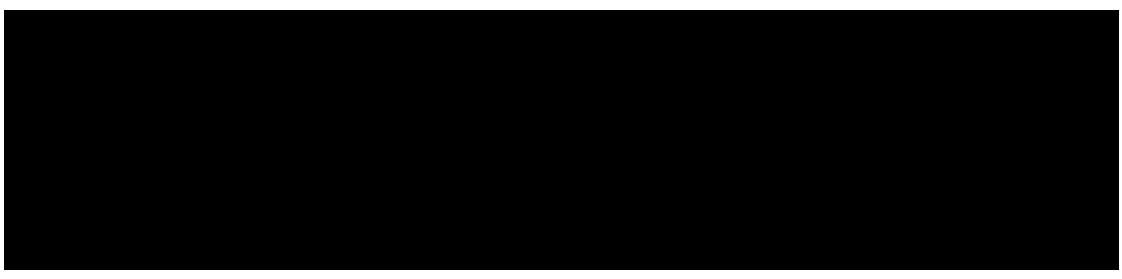
The safety analysis will include all patients who registered, received the Prizbind® for Intravenous Solution 2.5 g treatment and collected CRF except for who meet the ineligible criteria (see Section 9.7).

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Based on the concept of treatment emergent AEs, all AEs occurring between first intake of Prizbind® for Intravenous Solution 2.5 g prescribed at baseline visit up to 5 days after the last intake will be considered ‘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. Other AEs will be assigned to the screening or post-treatment period, respectively.

An AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as ‘related’.

The frequency and percentages of ADRs, SAEs, and other AEs occurred in treatment period as well as treatment + post-treatment period will be tabulated by system organ class and preferred term for all patients and for subgroups based on the important baseline characteristics (details will be described in the TSAP).

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.



[redacted]

9.8 QUALITY CONTROL

All processes are conducted according to GPSP SOPs <102-MLS-90-119>. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an estimate of the occurrence of the adverse events in the population under study. Due to the nature of a single cohort observational study, however, there are issues that may impose limitations in particular on the validity of the assessment based on the study data such as selection bias, loss to follow up, channeling bias and information and recall bias. Thus, comparisons and causal conclusions cannot be made, except for the investigator reported drug-related AEs. For patients enrolled in sites with the contract implemented after administration of Prizbind the information is limited to the information included in the medical chart which might lead to missing information.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

This PMS is to be conducted in accordance with both the in-house PMS SOP and working instructions which are in compliance with GPSP.

9.10.2 Study records

Paper CRFs for individual patients will be provided by the sponsor.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available. For CRFs, all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents for PMS is not allowed in Japan.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by Institutional Review Board (IRB) is not mandatory for conducting the PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (i.e., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives by the regulatory authorities.

~~11.~~ MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
An AE which possible leads to disability will be reported as an SAE.
Adverse Event of Special Interest (AESI)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this

study, e.g. the potential for AEs based on knowledge from other compounds in the same class.
No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the CRF:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome,

All ADRs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).

- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Prizbind®, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.
In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed

The investigator will report the Pregnancy Monitoring Forms as soon as possible via the unique entry point described in the Site Materials.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate CRF pages.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Prizbind® according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE

occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

AEs occurring from the patients whom used Prizbind after 15 April 2019 will not be collected in the CRF. These events will be reported spontaneously according to local regulations.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim and final results will be submitted to PMDA in Japanese Periodic Safety Update Report (PSUR) and re-examination documents. And the interim and final results including case reports are also planned to be used for related publications.

13. REFERENCES

13.1 PUBLISHED REFERENCES

Not applicable

13.2 UNPUBLISHED REFERENCES

c03666927-01 Clinical trial report – interim analysis. Idarucizumab (BI 655075). 1321.3. A
Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. RE-VERSE-AD (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran) trial.Interim analysis based on request from Japanese regulatory authorities.15 Jan 2016.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not applicable