Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on Boehringer Ingelheim’s Policy on Transparency and Publication of Clinical Study Data.

The synopsis is supplied for informational purposes only in the interests of scientific disclosure. It must not be used for any commercial purposes and must not be distributed, published, modified, reused, posted in any way, or used for any other purpose without the express written permission of Boehringer Ingelheim.
### Clinical Trial Report

**BI Trial No.: 1321.5**

**Synopsis**

<table>
<thead>
<tr>
<th>Name of Company:</th>
<th>Boehringer Ingelheim</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BI Proprietary Name:</strong></td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>BI Investigational Product:</strong></td>
<td>Idarucizumab, BI 655075</td>
</tr>
<tr>
<td><strong>Report Date:</strong></td>
<td>14 January 2015</td>
</tr>
<tr>
<td><strong>Trial No. / Doc. No.:</strong></td>
<td>1321.5/ c03026940-01</td>
</tr>
<tr>
<td><strong>Dates of Trial:</strong></td>
<td>10 Jan 2014 – 10 Aug 2014</td>
</tr>
<tr>
<td><strong>Date of Revision:</strong></td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Title of Trial:** Randomised, double-blind within dose groups, placebo-controlled Phase I trial in healthy Japanese male volunteers to investigate safety, tolerability and pharmacokinetics of different doses of BI 655075 (part 1) and to explore the effective dose of BI 655075 to reverse dabigatran anticoagulant activity (part 2)

**Principal/Coordinating Investigator:**

**Trial Sites:**

| Japan |

**Publications:** Data from this trial have not been published.

**Clinical Phase:** I

**Objectives:**

- To investigate safety and tolerability of different intravenous doses of idarucizumab administered alone and at or close to the steady state of dabigatran
- To investigate pharmacokinetics of idarucizumab and to explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran

**Methodology:**

Randomised, double-blind within dose groups, placebo controlled, sequential rising order, single centre trial. The Part 2 was initiated after evaluation of the safety data in the Part 1

**No. of Subjects:**

<table>
<thead>
<tr>
<th>Planned:</th>
<th>Entered: 80 subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actual:</td>
<td>Enrolled: 81 subjects</td>
</tr>
<tr>
<td></td>
<td>Entered: 80 subjects</td>
</tr>
</tbody>
</table>

In the Part 1, 8 subjects each were in the dose group 1 (idarucizumab 1000 mg as 5 minutes [min] infusion), the dose group 2 (idarucizumab 2000 mg as 5 min infusion), the dose group 3 (idarucizumab 4000 mg as 5 min infusion), and the dose group 4 (idarucizumab 8000 mg as 1 hour [h] infusion): 6 subjects on idarucizumab and 2 subjects on placebo in a dose group

| Entered: 32 | Treated: 32 | Analysed (for a primary endpoint): 32 |
Actual:
(continued)
In the Part 2, 12 subjects each were in the dose group 5 (dabigatran etexilate followed by idarucizumab 1000 mg as 5 min infusion), the dose group 6 (dabigatran etexilate followed by idarucizumab 2000 mg as 5 min infusion), the dose group 7 (dabigatran etexilate followed by idarucizumab 4000 mg as 5 min infusion), and the dose group 8 (dabigatran etexilate followed by idarucizumab 2500 mg as 5 min infusion + idarucizumab 2500 mg as 5 min infusion with a 15 min interval): 9 subjects on idarucizumab and 3 subjects on placebo in a dose group

Entered: 48  Treated: 48  Analysed (for a primary endpoint): 48

Diagnosis: Healthy Japanese male subjects

Main Criteria for Inclusion:
age ≥20 and ≤45 years, body mass index (BMI) ranging ≥18.5 and <25.0 kg/m²

BI Investigational Product: Idarucizumab, BI 655075

Dose: 50 mg/mL in buffer solution for infusion
In the Part 1, for the dose groups 1 to 4, a single dose of 1000 mg, 2000 mg, or 4000 mg as 5 min infusion; a single dose of 8000 mg as 1 h infusion
In the Part 2, for the dose groups 5 to 8, a single dose of 1000 mg, 2000 mg, or 4000 mg as 5 min infusion at or close to the steady state of dabigatran; and 2 doses of 2500 mg as 5 min infusion with a 15 min interval at or close to the steady state of dabigatran

Mode of Admin.: Intravenous infusion
Batch No.: B131002961

BI Investigational Product: Dabigatran etexilate (only as non-investigational medicinal product [NIMP] in the Part 2)

Dose: 4 day dosing schedule of 220 mg (110 mg capsule x 2) twice daily (b.i.d.) for 3 days and once daily (q.d.) for 1 day started on Days 1 and 8 in the Part 2

Mode of Admin.: Orally
Batch No.: B131002962
# Overview

**Name of company:** Boehringer Ingelheim  
**BI Proprietary Name:** Not applicable  
**BI Investigational Product:** Idarucizumab, BI 655075  
**Report Date:** 14 January 2015  
**Trial No. / Doc. No.:** 1321.5/ c03026940-01  
**Dates of Trial:** 10 Jan 2014 – 10 Aug 2014  
**Date of Revision:** Not applicable

## Comparator Product
- **Comparator Product:** Matching placebo (0.9% weight/volume sodium chloride) for idarucizumab
- **Dose:** Not applicable
- **Mode of Admin.:** Intravenous infusion
- **Batch No.:** B131002963

## Duration of Treatment
- **Idarucizumab:** a single dose infusion on Day 1 for the dose groups 1 to 4 in the Part 1; a single dose infusion on Day 11 for the dose groups 5 to 7 and 2 doses of infusion with a 15 min interval on Day 11 for the dose group 8 in the Part 2
- **Dabigatran etexilate (only in the Part 2):** 14 doses (b.i.d. on Days 1, 2, 3, 8, 9, and 10; and q.d. on Days 4 and 11 in the Part 2)

## Criteria for Evaluation
### Safety
- **Primary endpoint:** The number (%) of subjects with drug-related adverse events (AEs) assessed by the investigator to assess the safety and tolerability of idarucizumab administered alone (Part 1) or idarucizumab administered at or close to the steady state of dabigatran (Part 2)
- **Safety assessment:** Adverse events, laboratory tests (including haematology, clinical chemistry, urinalysis, coagulation parameters, cytokines, and antidrug antibodies [ADA]), vital signs (blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), and local tolerability

### Clinical Pharmacology
- **Secondary endpoints:**
  - Pharmacokinetic parameters
    - Parts 1 and 2 (the dose groups 1 to 8):
      - $C_{\text{max}}$, $\text{AUC}_{0-\infty}$, $\text{Ae}_{0-24}$ for idarucizumab ($\text{Ae}_{0-72}$ for the dose group 4)
    - Part 2 (the dose groups 5 to 8):
      - $\text{Ae}_{0-24}$ on Days 4 and 11 for sum dabigatran
      - $\text{AUC}_{2-12}$ on Days 4 and 11 for unbound sum dabigatran
  - Pharmacodynamic parameter
    - Part 2 (the dose groups 5 to 8):
      - $\text{AUEC}_{2-12}$ on Days 4 and 11 for diluted thrombin time (dTT)
**Trial Subjects and Compliance with Trial Protocol:**

In the Part 1, all the 32 subjects who were enrolled in the trial were randomly assigned to receive idarucizumab or placebo in the order of the dose group 1 to the dose group 4. Each dose group consisted of 8 subjects: 6 subjects for idarucizumab and 2 subjects for placebo. In the dose group 1, 6 subjects took idarucizumab 1000 mg (5 min infusion) and 2 subjects took placebo. In the dose group 2, 6 subjects took idarucizumab 2000 mg (5 min infusion) and 2 subjects took placebo. In the dose group 3, 6 subjects took idarucizumab 4000 mg (5 min infusion) and 2 subjects took placebo. In the dose group 4, 6 subjects took idarucizumab 8000 mg (1 h infusion) and 2 subjects took placebo. All the subjects in the dose groups 1 to 4 completed an observation period and a follow-up.

In the Part 2, of the 49 subjects who were enrolled in the trial, 1 subject was withdrawn from the trial because of AEs after taking dabigatran and he was not randomised. A total of 48 subjects were randomly assigned to receive idarucizumab or placebo in the order of the dose group 5 to the dose group 8 to take idarucizumab or placebo. Each dose group consisted of 12 subjects: 9 subjects for idarucizumab and 3 subjects for placebo. In the dose group 5, 9 subjects took idarucizumab 1000 mg (5 min infusion) and 3 subjects took placebo. In the dose group 6, 9 subjects took idarucizumab 2000 mg (5 min infusion) and 3 subjects took placebo. In the dose group 7, 9 subjects took idarucizumab 4000 mg (5 min infusion) and 3 subjects took placebo. In the dose group 8, 9 subjects took idarucizumab 5000 mg (2500 mg + 2500 mg [5 min + 5 min with a 15 min interval]) and 3 subjects took placebo. All the subjects in the dose groups 5 to 8 completed an observation period and a follow-up.

**Important protocol violations**

No subject had an important protocol violation in this trial.

**Demographic and baseline characteristics**

In the Part 1, the mean (SD) age was 30.5 (8.5) years and the mean (SD) BMI was 22.07 (1.88) kg/m². All subjects were Asian (Japanese) men. Of the 32 subjects, 8 (25.0%) subjects were previous smokers and 7 (21.9%) subjects were current
smokers at the start of the trial. No subjects were drinkers.

In the Part 2, the mean (SD) age was 25.1 (3.1) years and the mean (SD) BMI was 21.15 (1.72) kg/m². All subjects were Asian (Japanese) men. Of the 48 subjects, 6 (12.5%) subjects were previous smokers and 12 (25.0%) subjects were current smokers at the start of the trial. No subjects were drinkers.

Both in the Part 1 and in the Part 2, the mean (SD) age was 27.3 (6.4) years.

Exposure

Part 1
As for idarucizumab, 6 subjects each in the dose groups 1 to 4 received 1 dose of idarucizumab: idarucizumab 1000 mg (5 min infusion) in the dose group 1, idarucizumab 2000 mg (5 min infusion) in the dose group 2, idarucizumab 4000 mg (5 min infusion) in the dose group 3, and idarucizumab 8000 mg (1 h infusion) in the dose group 4.

As for placebo, 2 subjects each in the dose groups 1 to 3 received 1 dose of placebo (5 min infusion) and 2 subjects in the dose group 4 received 1 dose of placebo (1 h infusion).

Part 2
As for idarucizumab, 9 subjects each in the dose groups 5, 6, and 7 received 1 dose of idarucizumab and 9 subjects in the dose group 8 received 2 doses of idarucizumab: idarucizumab 1000 mg (5 min infusion) in the dose group 5, idarucizumab 2000 mg (5 min infusion) in the dose group 6, idarucizumab 4000 mg (5 min infusion) in the dose group 7, and idarucizumab 2500 mg+2500 mg (5 min + 5 min infusion with a 15 min interval) in the dose group 8.

As for placebo, 3 subjects each in the dose groups 5, 6, and 7 received 1 dose of placebo (5 min infusion) and 3 subjects in the dose group 8 received 2 doses of placebo (5 min + 5 min infusion with a 15 min interval).

As for dabigatran etexilate, 12 subjects each in the dose groups 5 to 8 received 14 doses of dabigatran etexilate 220 mg before administration of idarucizumab or placebo.
Treatment compliance

The study medication was always given to the subject under direct supervision of the investigator or one of the investigator’s authorised designees.

Pharmacokinetics

Idarucizumab

In the Part 1, after administration of single dose of idarucizumab alone, $C_{\text{max}}$ was achieved around the end of infusion, followed by rapid biphasic decline in plasma concentrations. Exposure (AUCs and $C_{\text{max}}$) to idarucizumab increased dose-proportionally after single administration of idarucizumab 1000 to 8000 mg (for $C_{\text{max}}$, the 8000 mg dose group was excluded because of different infusion time). Inter-individual variability of idarucizumab exposure was low with geometric coefficient of variation (gCV) values ranging from 14.4 to 17.8% for AUCs and from 6.88 to 14.3% for $C_{\text{max}}$. The geometric mean (gMean) initial half-life ($t_{1/2,2}$) was short ranging from 0.629 to 1.04 h, and gMean $t_{1/2}$ ranged from 6.38 to 10.3 h and was dose-independent. The gMean $V_{\text{ss}}$ were approximately 6 to 7 L over the entire dose range, suggesting limited distribution of idarucizumab in blood compartment. Total plasma clearance was constantly 36 to 38 mL/min. The cumulative fraction excreted into urine increased from 7 to 41% with increasing dose after single administration of idarucizumab 1000 to 8000 mg, suggesting the saturation of renal uptake of idarucizumab. Renal clearance (CL$_R$) increased with increasing dose from 3.32 to 16.7 mL/min.

In the Part 2, after administration of single dose of idarucizumab at steady state of dabigatran, exposure, half-life, total plasma clearance, $V_{\text{ss}}$, were comparable with those obtained in the Part 1. $C_{\text{max}}$ increased sub-proportionally with dabigatran, whereas AUC$_{0-\infty}$ increased dose-proportionally. Urinary excretion (fe) and CL$_R$ with dabigatran were approximately 2 to 3 times higher than those without dabigatran for idarucizumab 1000 to 4000 mg, whereas they were comparable at highest dose of idarucizumab 8000 mg alone and 2500 mg+2500 mg with dabigatran.
Clinical Pharmacology Results: (continued)

Table 1

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Ida 1000 mg</th>
<th>Ida 2000 mg</th>
<th>Ida 4000 mg</th>
<th>Ida 8000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>gMean</td>
<td>gCV[%]</td>
<td>gMean</td>
<td>gCV[%]</td>
</tr>
<tr>
<td>AUC_{0-73}[\mu mol/h/L]</td>
<td>6/6/6/6</td>
<td>9150</td>
<td>15.0</td>
<td>18500</td>
</tr>
<tr>
<td>C_{\text{max}}[\mu mol/L]</td>
<td>6/6/6/6</td>
<td>6810</td>
<td>10.1</td>
<td>15700</td>
</tr>
<tr>
<td>A_{R1,2}[\mu mol/L]</td>
<td>6/6/6/6</td>
<td>1.54</td>
<td>54.9</td>
<td>6.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part 2</th>
<th>DE: 220 mg + Ida 1000 mg</th>
<th>DE: 220 mg + Ida 2000 mg</th>
<th>DE: 220 mg + Ida 4000 mg</th>
<th>DE: 220 mg + Ida 8000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>gMean</td>
<td>gCV[%]</td>
<td>gMean</td>
<td>gCV[%]</td>
</tr>
<tr>
<td>AUC_{0-73}[\mu mol/h/L]</td>
<td>9/9/9/9</td>
<td>8590</td>
<td>14.2</td>
<td>19200</td>
</tr>
<tr>
<td>C_{\text{max}}[\mu mol/L]</td>
<td>9/9/9/9</td>
<td>9510</td>
<td>33.8</td>
<td>17600</td>
</tr>
<tr>
<td>A_{R1,2}[\mu mol/L]</td>
<td>9/9/9/9</td>
<td>4.21</td>
<td>35.1</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Abbreviations: DE=dabigatran etexilate; Ida=idarucizumab; gMean=geometric mean; gCV=geometric coefficient of variation

1 A_{R1,2}[\mu mol/L] for idarucizumab 8000 mg

Dabigatran

Plasma concentrations of sum dabigatran and unconjugated dabigatran rapidly increased after the end of idarucizumab infusion. Approximately 5 to 6-fold increase was observed in plasma concentrations in all dose groups. In comparison with urinary excretion in the absence of idarucizumab, urinary excretion was transiently reduced in the presence of idarucizumab and reached the range of placebo treated subjects at the end of collection interval. gMean cumulative excretions into urine were approximately 5.6 to 7.9% for sum dabigatran and 5.2 to 7.4% for unconjugated dabigatran at 74 h after the last administration of dabigatran etexilate.

Concentration of unbound sum dabigatran and unbound dabigatran decreased to below the limit of quantification (BLQ) immediately after administration of single dose of idarucizumab. When 5000 mg of idarucizumab was administered as 2500 mg+2500 mg (5 min + 5 min infusion with a 15 min interval), decrease to BLQ was observed after the first administration of 2500 mg in all subjects. Redistribution of unbound sum dabigatran and unbound dabigatran were observed dose-dependently. It started earlier in the low dose groups (1000 mg and 2000 mg) and later in high dose groups (4000 mg and 2500 mg+2500 mg). AUC of unbound sum dabigatran and unbound dabigatran decreased with increasing idarucizumab.
Clinical Pharmacology
Results:
(continued)

doses.

Table 2

<table>
<thead>
<tr>
<th>DE 220 mg</th>
<th>DE 220 mg/placebo</th>
<th>DE 220 mg + Ida 1000 mg</th>
<th>DE 220 mg + Ida 2000 mg</th>
<th>DE 220 mg + Ida 4000 mg</th>
<th>DE 220 mg + Ida 2500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Day 4)</td>
<td>(Day 11)</td>
<td>(Day 11)</td>
<td>(Day 11)</td>
<td>(Day 11)</td>
<td>(Day 11)</td>
</tr>
</tbody>
</table>

| gMean [μg] | 1050  | 960 | 1250 | 1310 | 930 | 1060 |
| (gCV[%])  | (17.8) | (27.9) | (32.0) | (30.1) | (41.0) | (28.1) |

<table>
<thead>
<tr>
<th>Unbound sum dabigatran</th>
<th>AUC&lt;sub&gt;12,18&lt;/sub&gt;</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE 220 mg + Ida 4000 mg</td>
<td>DE 220 mg + Ida 2500 mg</td>
<td></td>
</tr>
<tr>
<td>(Day 11)</td>
<td>(Day 11)</td>
<td></td>
</tr>
</tbody>
</table>

| gMean [μg/L] | 998  | 999 | 330 | 82.2 | 10.1 | 10.0 |
| (gCV[%])    | (45.3) | (34.8) | (109) | (149) | (1.86) | (0.0213) |

Abbreviations: DE=dabigatran etexilate; Ida=idarucizumab; gMean=geometric mean; gCV=geometric coefficient of variation

Pharmacokinetics and pharmacodynamics
A close linear relationship was observed between unbound sum dabigatran plasma concentration and activated partial thromboplastin time (aPTT), dTT, thrombin time (TT), and ecarin clotting time (ECT). Diluted TT correlated most closely with unbound sum dabigatran.

Pharmacodynamics
Effect of idarucizumab on coagulation parameters and potential prothrombotic effect
In the Part 1, no differences were found in the values of coagulation parameters of dTT, ECT, TT, aPTT, and activated clotting time (ACT) between before and after administration of idarucizumab. No effect of idarucizumab was observed on endogenous thrombin potential (ETP), D-Dimer, and F1.2 as well. Thus, idarucizumab did not exhibit an effect on coagulation parameters or did not have a prothrombotic effect.
### Reversal effect of idarucizumab on dabigatran-induced clotting time prolongation

In the Part 2, to assess the reversal effect of idarucizumab on dabigatran-induced clotting time prolongation, upper limit of normal (ULN) reference values were determined on the basis of the mean + 2 SD of all individual baseline measurements. On Day 4, dabigatran administration resulted in prolongation of clotting times as measured by all coagulation parameters. On Day 11, all coagulation parameters demonstrated an immediate and complete reversal below ULN in all groups after administration of idarucizumab 1000 mg to 2500 mg+2500 mg. Duration of reversal depended on the administered dose of idarucizumab.

Partial return of anticoagulant effect was associated with redistribution of unbound sum dabigatran, and it occurred around 1 to 24 h after administration of idarucizumab 1000 mg or 2000 mg. Immediate, complete, and sustained reversal was observed after administration of idarucizumab 4000 mg and 2500 mg+2500 mg over the entire measurement period until 72 h, on the basis of dTT, ECT, aPTT, and ACT. For TT, a slight elevation of mean clotting time above the ULN was observed between 24 and 48 h after administration of idarucizumab 4000 mg and 48 h after administration of idarucizumab 2500 mg+2500 mg, respectively. On the basis of evaluation of ACT, idarucizumab 2000 mg could lead to an immediate, complete, and sustained reversal over the entire measurement period up to 72 h after administration of idarucizumab. It should be noted that ACT dropped substantially below the mean baseline immediately after the end of infusion of idarucizumab.

Taken together, the results of clotting time measurements indicated that administration of idarucizumab 4000 mg and 2500 mg+2500 mg resulted in immediate, complete, and sustained reversal of dabigatran-induced clotting time prolongation.

The reversal of dabigatran anticoagulation was also demonstrated by the ratio between the mean area under the effect curve with consideration of baseline (AUEC<sub>above,2-12</sub>) on Days 4 and 11.
Safety Results:

**Adverse events**

Safety data were analysed for all patients who took at least 1 dose of idarucizumab or placebo (the treated set).

In this trial, a primary endpoint was the number (%) of subjects with drug-related AEs assessed by the investigator.

Of 32 subjects in the Part 1, 1 (16.7%) of the 6 subjects who received 5 min placebo infusion was reported with an AE, increased blood creatine phosphokinase, which was mild in intensity and assessed as drug-related by the investigator, and none of the subjects who received 1 h placebo infusion or any dose of idarucizumab were reported with an AE. Of 48 subjects in the Part 2, no subjects were reported with an AE.

Both in the Part 1 and the Part 2, no subjects experienced severe AEs, serious AEs, other significant AEs (according to International Conference on Harmonisation [ICH] E3), or protocol-specified AEs of special interest; no subjects discontinued taking study medication; and no death was reported.

**Other safety parameters**

In the Part 1, increase of creatinine kinase was reported for 1 subject on 5 min placebo infusion in the Part 1. The increase in the subject was unaccompanied by elevation of creatine kinase-MB (CK-MB), and the value for creatinine kinase was
**Safety Results:** returned to normal at follow-up visits.

In the Part 1 and the Part 2, after infusion of idarucizumab, values of low molecular weight proteins and urine proteins increased dose-dependently, but returned to a normal reference range within 4 to 12 h.

In the Part 1 and the Part 2, other parameters did not show any clinically relevant changes throughout the trial. No apparent increases in liver parameters including bilirubin were seen throughout the trial. No clinically relevant changes were observed in ECG, vital signs, or local tolerability of infusion.

**Antidrug antibodies**

*Anti-idarucizumab antibodies*

At the predose visit, before infusion of idarucizumab or placebo, pre-existing antibodies with cross-reactivity to idarucizumab were detected in 14 of 80 subjects in the Part 1 and the Part 2: 4 of the 20 subjects on placebo and 10 of the 60 subjects on idarucizumab. For 2 of the 10 subjects on idarucizumab who were positive before drug administration, anti-idarucizumab antibody titers increased at the 3-month follow-up time point relative to the titers determined at the earlier time points. No obvious effects of pre-existing anti-idarucizumab antibodies were found for the pharmacokinetics of idarucizumab.

The formation of treatment-emergent anti-idarucizumab antibodies was found in 4 of 60 subjects on idarucizumab on the basis that no positive titer was found at baseline and a positive titer was found at 1 or more time points in the post-treatment: 2 subjects had a transient treatment-emergent anti-idarucizumab antibody response, without a positive titer at the last sampling point (3-month follow-up) and 2 subjects had responses classified as possibly persistent because anti-idarucizumab antibodies were still detected at the last sampling point.

Regarding epitope specificity of the anti-idarucizumab antibodies, of the 18 subjects with anti-idarucizumab, 13 subjects had antibodies with specificity towards a C-terminus epitope, 3 subjects had antibodies with specificity initially towards a C-terminus epitope but switched to a mixed specificity (C-terminus, constant region and/or variable region), 1 subject had an antibody with specificity initially towards a C-terminus epitope but switched to a primarily anti-variable region specificity, and 1 subject had no antibodies at baseline but an antibody with a mixed specificity at the last sampling point (3-month follow-up).
### Conclusions:

$C_{\text{max}}$ of idarucizumab was achieved at around the end of infusion, followed by biphasic elimination with a rapid initial phase and a longer terminal phase. Exposure ($C_{\text{max}}$ and $\text{AUC}_{0-\infty}$) to idarucizumab increased dose-proportionally. Volume of distribution was small and total plasma clearance was constant. The cumulative fraction excreted into urine increased with increasing dose. Pharmacokinetics of idarucizumab was almost comparable with or without dabigatran. Exceptionally, urinary excretion ($fe$) and $CL_R$ with dabigatran was approximately 2 to 3 times higher than those without dabigatran.

Immediate, complete reversal was observed on the basis of unbound fraction of dabigatran and coagulation parameters of aPTT, dTT, ECT, TT, and ACT after administration of idarucizumab at steady state of dabigatran in all dose groups, and reversal effect was sustained at therapeutic dose of 4000 mg and 2500 mg+2500 mg.

Administration of idarucizumab (a single dose infusion of 1000 mg for 5 min, 2000 mg for 5 min, 4000 mg for 5 min, or 8000 mg for 1 h) and administration of idarucizumab (a single dose infusion of 1000 mg for 5 min, 2000 mg for 5 min, 4000 mg for 5 min, or 2 doses of infusion of 2500 mg each for 5 min with a 15 min interval) at the steady state of dabigatran were safe and well tolerated, and had a low level of immunogenicity in healthy Japanese male subjects.