# Clinical Trial Protocol

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| | **Document Number:** | **c16458864-01** |
| **BI Trial No.:** | 1321-0019 | |
| **BI Investigational Product(s):** | Idarucizumab （BI655075） | |
| **Title:** | A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. | |
| **Lay Title:** | This study looks at the effects of idarucizumab in patients who take dabigatran and need emergency surgery or are bleeding | |
| **Clinical Phase:** | III | |
| **Trial Clinical Monitor:** | [redacted]<br>Phone: [redacted] Fax: [redacted] | |
| **Principal Investigator < or > Coordinating Investigator:** | [redacted]<br>Phone: [redacted] | |
| **Status:** | Final Protocol | |
| **Version and Date:** | **Version:** | **Date:** |
| | 1 | 01 June 2017 |

# CLINICAL TRIAL PROTOCOL SYNOPSIS

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|---|---|
| **Company name** | Boehringer Ingelheim |
| **Finished product name** | Idarucizumab |
| **Active ingredient name:** | Idarucizumab （BI655075） |
| **Protocol date** | 01 June 2017 |
| **Revision date** | |
| **Trial number** | 1321-0019 |
| **Title of trial:** | A Phase III, case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. |
| **Principal Investigator < for single-centre trial or > Coordinating Investigator< for multi-centre trial if applicable >:** | [redacted]<br>Phone: [redacted] |
| **Trial site(s):** | Multi-centre trial |
| **Clinical phase:** | III |
| **Objective(s):** | The primary objective is to demonstrate reversal of the anticoagulant effect of dabigatran. The secondary objectives are the assessment of bleeding, clinical outcomes and safety and the pharmacokinetics of dabigatran in the presence of idarucizumab. |
| **Methodology:** | Open label, uncontrolled, case series |
| **Number of patients entered:** | 20 |
| **Number of patients** | 20 |

| | |
|---|---|
| **on each treatment:** | |
| **Diagnosis :** | There are two separate groups of patients with different diagnoses:<br><br>**Group A.** Patients who are taking dabigatran etexilate and have uncontrolled or life-threatening bleeding requiring urgent medical or surgical intervention<br><br>**Group B.** Patients who are taking dabigatran etexilate who may not be bleeding, but do require an emergency surgery or other invasive procedure for a condition other than bleeding, where therapeutic anticoagulation with dabigatran etexilate is undesirable |
| **Main in- and exclusion criteria** | • Group A-Dabigatran etexilate -treated patients seen in the Emergency Department (ED) or similar department of a hospital who exhibit signs and symptoms of (overt) uncontrolled bleeding requiring urgent medical or surgical intervention.<br><br>OR<br><br>• Group B-Dabigatran etexilate treated patients seen in the Emergency Department or similar department of a hospital who require emergency surgery or other medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure.<br><br>AND<br><br>Establish that the patient is being treated with dabigatran etexilate. |
| **Test product(s):** | Idarucizumab in buffered solution for injection, 50 mL/vial, 50 mg/mL |
| **dose:** | The total dose is 5 g (two 2.5g vials). A single vial contains 2.5g of idarucizumab. Patients will receive a 2.5g vial of study medication and a second 2.5g vial within the next 15 minutes. In rare instances, an additional 5 g dose is justified. |
| **mode of administration:** | Intravenous |
| **Comparator products:** | Not applicable |
| **dose:** | Not applicable |

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|---|---|
| **mode of administration:** | Not applicable |
| **Duration of treatment:** | Two vials of idarucizumab administered no more than 15 minutes apart. |
| **Endpoints** | Efficacy will be based on central laboratory determination of reversal of the anticoagulant effect of dabigatran, using several coagulation tests (thrombin time (TT), diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and local assessment of aPTT. No dosing or patient management decisions are based on central lab determination of reversal. Dosing of idarucizumab will not be affected by a local lab test.<br><br>**Primary endpoint:**<br><br>The primary study endpoint is the maximum reversal of the anticoagulant effect of dabigatran, based on central laboratory determination of dTT or ECT, at any time point from the end of the first infusion up to 4 hours after the completion of the second infusion.<br><br>**Secondary endpoints:**<br><br>• Time to cessation of bleeding (for Group A only) since first infusion up to 24 hours after the completion of second infusion. Bleeding status will be categorized before and at several time points after treatment.<br><br>• Occurrence of major bleeding (for Group B only) intraoperatively and up to 24 hours post-surgery.<br><br>• Minimum unbound sum (free) dabigatran concentrations at any time point since end of the first infusion up to 4 hours after the completion of the second infusion.<br><br>• Reversal of aPTT and TT, at any time point since end of the first infusion up to 4 hours after the completion of the second infusion. |
| **Safety criteria:** | Adverse events, local tolerability, immune reactions, thrombotic events, mortality, vital signs (BP, PR), laboratory tests (including hepatic and renal function, hematology, clinical chemistry, coagulation parameters, cytokines and ADA(anti-idarucizumab antibody)). |

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| | Type and location of bleeding will be evaluated. |
| **Statistical methods:** | Descriptive statistics for efficacy, safety and PK/PD endpoints will be calculated. Confidence limits will be provided when appropriate. The two patient groups (bleeding patients and those requiring emergency surgery/procedures) will be analysed separately and together, with an overall conclusion, if possible. Among bleeding patients, those with intracranial hemorrhage (ICH) will be analyzed separately in deference to expected differences in management strategies and functional outcomes in these patients vs those with other hemorrhagic diagnoses. [redacted] Other subgroups of bleeds of similar type (e.g. gastrointestinal, trauma) will be analysed separately where cohort size permits. |

# FLOW CHART

| **Investigations/Tests and Procedures** | **Screening Period** | **Treatment Period** | | **Safety Follow-Up Period** | | |
|---|---|---|---|---|---|---|
| **Visit Number** | **1** | **2.1** | **2.2** | **3** | **4** | **5 (End of study)** |
| **Visit Description** | Patient screening | Vial 1 | Vial 2 | 24-hours after vial 2 | 7 days after vial 2 | 30 days after vial 2 |
| **Visit Day(s)** | 1 | 1 | 1 (no later than 15 min after vial 1) | 2 (± 2 hours) | 7 (± 3 days) | 30 (±7 days) |
| Informed consent[1,2] | X | | | | | |
| Inclusion / exclusion criteria | X | | | | | |
| Confirm dabigatran etexilate use | X | | | | | |
| Medical History | X | | | | | |
| Demographics | X | | | | | |
| Physical Exam[16] and Vital Signs, Temperature[2] | X[9] | X[13,14] | X [13,14] | X[13,14] | X[13,14,9] | X[13] |
| Bleed assessment[3,4] | X | X | X | X | X | X |
| Surgery/Procedure assessment[4] | X | X | X | X | X | X |
| Study Drug Administration[5] | | X | X | | | |
| PK/PD Blood Draw[6] | X | | X | X | | X |
| Local Safety Blood Draw | X[10,11,12] | | X[11] | X[10,12] | | |
| Pregnancy Testing[7,2] | X | | | | | X |
| Study drug accountability | | | X | | | |
| ECG[2] | X | | | | X | |
| Adverse Events[4] | X | X | X | X | X | X |
| Concomitant therapies | X | X | X | X | X | X |
| [redacted] | | | | | | |
| Conclusion of patient participation[8] | | | | | | X |

1- Written informed consent.

2- Due to the need for urgent care in these patients, collection of medical history and other standard of care information (e.g. laboratory values, vital signs, weight, ECG) within 24 hours prior to inform consent may be collected on the CRF in order to prevent unnecessary repetition of procedures.

3- Four bleeding assessment classifications: 1) ISTH, 2) TIMI, 3) GUSTO, 4) Glasgow Coma Scale (for ICH patients)

4- Sites may be requested to provide redacted source documents for specified adverse events. These source documents may include, but are not limited to: progress notes, discharge summaries, lab results, ECGs, consult reports, autopsy report, MRI or CT scans and other test results.

5- In rare instances during the same hospitalization, e.g. 2 to 24 h after the initial 5 g dose, a patient may experience a re-start of bleeding or have a potential for a life-threatening bleed or have a need for an additional emergency surgery/procedure, coupled with re-elevation of local clotting tests. In such cases an additional 5 g dose is justified and the patient should be allocated a new patient number. Blood sampling times are the same as with the first 5 g dose or as logistics permit (Prior to administration of the third vial, just prior to the fourth vial, as well as between 10 and 30 min, 1, 2, 4, 12, 24 hours, and 30 days after the end of the infusion of the fourth vial). Other study procedures and tests should be performed per protocol.

6- Blood sampling for central PD (biomarker) and pharmacokinetic (PK) measurements and/or anti-drug antibodies will occur: Prior to administration of the first vial, just prior to the second vial, as well as between 10 and 30 min, 1, 2, 4, 12, 24 hours, and 30 days after the end of the infusion of the second vial. For details refer to Table 5.3.2.1: 1. Time will be recorded for every blood sample taken. Actual time for the start and end of the infusion will be recorded.

7- Local urine or other appropriate spot pregnancy test in women of childbearing potential. Recruitment of pregnant patients is allowed only after a careful evaluation/discussion of the risks and benefits of study participation between the treating physician and patient, unless it is against local regulations.

8- Conclusion of patient participation also needs to be completed if the patient withdraws prematurely following first vial of study medication.

9- Includes modified Rankin Scale (mRS) assessment for ICH cohort only

10- Includes Hematology and Chemistry

11- Draw blood for local lab aPTT at baseline, just prior to the second vial, 10 to 30 minutes, and 12 hour after second vial.

12- Additional local lab testing may be done at the discretion of the treating physician to facilitate patient clinical management.

13- Blood pressure, heart rate only.

14- Blood pressure and heart rate hourly while the patient is in the emergency or similar department, then every 4 hours for the next 72 hours or until discharge.

[redacted]

16- A physical examination includes height and body weight and height will only be collected on visit 1.

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# ABBREVIATIONS

| | |
|---|---|
| ACT | Activated Clotting Time |
| ADAs | Anti-drug Antibodies |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALQ | Above the Lower Limit of Quantification |
| ALT | Alanine Transaminase |
| AST | Aspartate Transaminase |
| AUC | Area under the Curve |
| aPTT | Activated Partial Thromboplastin Time |
| BI | Boehringer Ingelheim |
| BI 655075 | Idarucizumab |
| BID | Twice Daily |
| BLQ | Below the Lower Limit of Quantification |
| BP | Blood Pressure |
| $C_{pre}$ | Concentration of the Analyte in Plasma Prior to First Dose |
| $C_{max}$ | Concentration Maximum |
| CA | Competent Authority |
| CHO | Chinese Hamster Ovary Cells |
| CML | Clinical Monitor Local |
| CRA | Clinical Research Associate |
| CRF | Case Report Form |
| CTR | Clinical Trial Report |
| DE | Dabigatran Etexilate |
| DILI | Drug Induced Liver Injury |
| dTT | Diluted Thrombin Time |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| ECT | Ecarin Clotting Time |
| ED | Emergency Department |
| ECL | Electro Chemiluminescence |
| EDTA | Ethylendiaminetetracetic Acid |
| ELISA | Enzyme-Linked Immunosorbant Assay |
| EudraCT | European Clinical Trials Database |
| Fab | Monoclonal Antibody Fragment |
| FDA | Food and Drug Administration |
| FFP | Fresh frozen plasma |
| GCS | Glasgow Coma Scale |
| GCP | Good Clinical Practice |
| GUSTO | Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries |
| HPLC-MS/MS | High Performance Liquid Chromatography, Tandem Mass Spectrometry |
| HR | Heart Rate |
| ICH | Intracranial Hemorrhage |
| ICU | Intensive Care Unit |
| IEC | Independent Ethics Committee |

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|---|---|
| INR | International Normalised Ratio |
| IRB | Institutional Review Board |
| ISF | Investigator Site File |
| ISTH | International Society for Thrombosis and Hemostasis |
| i.v. | Intravenous |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web-based Response System |
| LAR | Legally Authorized Representative |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| mg | Milligram |
| NC | Not Calculated |
| NOA | Not Analysed |
| NOAEL | No Observed Adverse Effect Level |
| NOP | No Peak Detectable |
| NOR | No Valid Result |
| NOS | No Sample Available |
| OPU | Operative Unit |
| PCC | Prothrombin Complex Concentrates |
| PD | Pharmacodynamics (equivalent to biomarkers) |
| PK | Pharmacokinetics |
| p.o. | per os (oral) |
| PR | Pulse Rate |
| PTT | Partial Thromboplastin Time |
| RBC | Red Blood Cell |
| RDC | Remote Data Capture |
| RE-LY | Randomized Evaluation of Long-term Anticoagulant Therapy |
| RE-VERSE-AD | RE-VERSal Effects of Idarucizumab on Active Dabigatran |
| rFVIIa | Recombinant Factor VIIa |
| SAE | Serious Adverse Event |
| SD | Standard Deviation |
| SOP | Standard Operating Procedure |
| SUSARs | Suspected Unsuspected Serious Adverse Events |
| $t_{max}$ | Time From Dosing to Maximum Concentration |
| $t_{1/2}$ | Terminal Half-Life |
| TIMI | Thrombolysis in Myocardial Infarction |
| TSAP | Trial Statistical Analysis Plan |
| TT | Thrombin Time |
| ULN | Upper Limit of Normal |
| $V_{ss}$ | Distribution Volume in the Steady State |
| VTE | Venous Thrombotic Events |

# 1. INTRODUCTION

## 1.1 MEDICAL BACKGROUND

Anticoagulation therapy is a mainstay of treatment and prevention of pathologic thrombosis in different clinical settings. Several novel oral anticoagulants have been developed, with efficacy comparable to or better than Vitamin K antagonists such as warfarin. However, for all anticoagulants, bleeding, including life-threatening or fatal bleeding, remains a relevant side effect. With the increasing use of novel oral anticoagulants such as dabigatran, for patients with life-threatening or uncontrolled bleeding, reversal agents that could be used in rare or uncommon emergency situations to reverse the anticoagulant effects of these new drugs may offer additional benefits. An ideal antidote would be safe, specific, immediately effective, and easy to administer.

Dabigatran is the active principle of the prodrug dabigatran etexilate, a direct thrombin inhibitor, which has been shown to be effective for:

- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors.

The pivotal phase III trial for prevention of stroke and systemic embolism, RE-LY (U09-3249-02) (P09-11669), was conducted in over 18,000 patients with atrial fibrillation and demonstrated major bleeding rates of approximately 3%/year and life-threatening bleeding rates of approximately 1.5%/year for dabigatran etexilate 150 mg bid. The rate of major bleeding was numerically lower, and the rate of life-threatening bleeding was significantly lower than that of warfarin, even in the absence of a dabigatran antidote. Fatal bleeding occurred at a rate of approximately 0.2%/year for dabigatran and 0.3%/year for warfarin. Outcomes of major bleeding with dabigatran were as good or better than warfarin with a trend towards lower mortality for dabigatran-treated subjects (P13-12677).

Post marketing experience has confirmed that major and life-threatening bleeding, including fatal bleeding, have occurred in patients taking dabigatran etexilate since its approval (U11-2616-01). The estimated bleeding rates from post-marketing surveillance are not in excess of the rates of bleeding seen in the RE-LY trial and are similar to or lower than warfarin. Dabigatran associated bleeding has been normally managed with standard supportive care in most cases, with the possibility of hemodialysis in selected patients. Temporary discontinuation of dabigatran should occur if there is active pathological bleeding. Besides well established measures for treatment of bleeding certain patients could still benefit from additional measures such as immediate reversal of anticoagulation.

Recently, idarucizumab, a specific reversal agent for dabigatran, which is the subject of this investigational protocol, has become available in many countries for the management of dabigatran-associated bleeds that require more than supportive care and for patients being

treated with dabigatran who require emergency surgery or other procedures where there is a high risk of bleeding (P13-01830, P13-04186).

## 1.2 DRUG PROFILE

Drug Substance and Drug Product

Idarucizumab is a humanized Fab (antibody fragment) targeting the direct thrombin inhibitor dabigatran. Idarucizumab was generated from a mouse monoclonal antibody against dabigatran. The monoclonal antibody was humanized and reduced to a Fab.

Idarucizumab is manufactured from CHO cells, using standard mammalian cell culture and protein purification techniques. Purification has included an initial capture step (affinity chromatography) and additional chromatography steps to remove process related impurities, as well as virus inactivating and reducing steps such as acid treatment and nanofiltration.

The Drug Product is a solution for injection filled aseptically into sterile glass vials containing 50 mL with concentration 50 mg/mL (total 2,500 mg/vial).

Idarucizumab is a Fab designed to bind to dabigatran and remove its anticoagulant effect, thereby reversing anticoagulation in the patient. As such, idarucizumab contains no Fc component and is, therefore, devoid of reactions associated with Fc receptors, such as cytotoxic effect or functions through complement or interactions with Fcγ receptors or neonatal Fc receptors (FcRn).

Idarucizumab binds dabigatran with an affinity that is about 300 times as high as that observed with thrombin. Consequently, idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity. In healthy young volunteers with normal renal function, in volunteers who were 65 to 80 years of age, and in volunteers who were 45 to 80 years of age with mild or moderate renal impairment, the administration of idarucizumab produced immediate and complete reversal of the anticoagulant effects of dabigatran without procoagulant effects.(6-8) Given these findings, a prospective cohort study was undertaken to examine the efficacy and safety of idarucizumab for the reversal of the anticoagulant effects of dabigatran in patients who presented with serious bleeding or who required urgent surgery or intervention. The results from the first 90 patients enrolled in the study of the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) have been published and are summarized here.

Clinical Studies

RE-VERSE AD (P15-06362), a Clinical Study in Patients

We undertook a prospective cohort study to determine the safety of 5 g of intravenous idarucizumab and its capacity to reverse the anticoagulant effects of dabigatran in patients who had serious bleeding (group A) or required an urgent procedure (group B). The primary end point was the maximum percentage reversal of the anticoagulant effect of dabigatran

within 4 hours after the administration of idarucizumab, on the basis of the determination at a central laboratory of the dilute thrombin time or ecarin clotting time. A key secondary end point was the restoration of hemostasis.

RESULTS

This interim analysis included 90 patients who received idarucizumab (51 patients in group A and 39 in group B). Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval, 100 to 100). Idarucizumab normalized the test results in 88 to 98% of the patients, an effect that was evident within minutes. Concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients in group A who could be assessed, hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients in group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.

CONCLUSIONS

Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

Based on data from RE-VERSE AD, it is expected that the vast majority of patients will only be treated once. Additional exposure to the antidote, for a new event that may be weeks or even years after the first event, is expected to be infrequent or rare. In rare instances during the same hospitalization, e.g. 2 to 24 h after the initial 5 g dose, a patient may experience a re-start of bleeding or have a potential for a life-threatening bleed or have a need for an additional emergency surgery/procedure, coupled with re-elevation of local clotting tests. In such cases, an additional 5 g dose is justified.

Phase I data

Pharmacology

Idarucizumab binds to dabigatran with an affinity (Kd) of 2.7 pM. This is ~270-fold more potent than the binding affinity of dabigatran for thrombin. It was also tested in vitro in human plasma using a modified thrombin time assay (Figure 1.2: 1, left). First dabigatran was added in a known concentration (7 nM) to prolong the thrombin clotting time (set to 100%). Increasing concentrations of idarucizumab were then added and reversal of the clotting time was measured. Figure 1.2: 1, left, illustrates the reversal of the thrombin clotting time by idarucizumab, with an IC50 of 2.4 nM. Further studies using human whole blood (Figure 1.2: 1, right), illustrate a reversal effect of dabigatran similar to that in plasma, indicating low non-specific binding of idarucizumab to other cellular components in blood.

A. Plasma: B. Whole Blood:

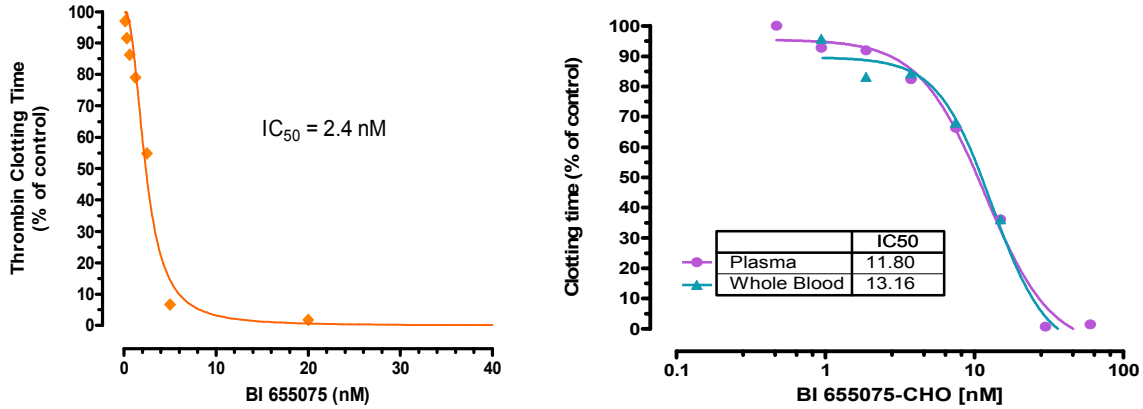



Figure 1.2: 1: The reversal of anticoagulant activity of dabigatran by BI 655075 (idarucizumab) in human plasma (A) and whole blood (B).

Source data U13-1986-01

Reversal of anticoagulation was tested in a rat model in vivo. Dabigatran was given as an initial bolus with continuous infusion to achieve steady state plasma levels of ~ 190 ng/ml. When measuring the thrombin time ex vivo, dabigatran prolonged the thrombin time to approximately 100 seconds from a baseline of 25 seconds (Figure 1.2: 2). Giving a single bolus of idarucizumab at an equimolar dose at t=0 completely reversed the anticoagulant activity of dabigatran within one minute to baseline. This reversal by a single bolus of idarucizumab was maintained for the 30 minute dabigatran infusion. Measurement of aPTT also resulted in a similar pattern.

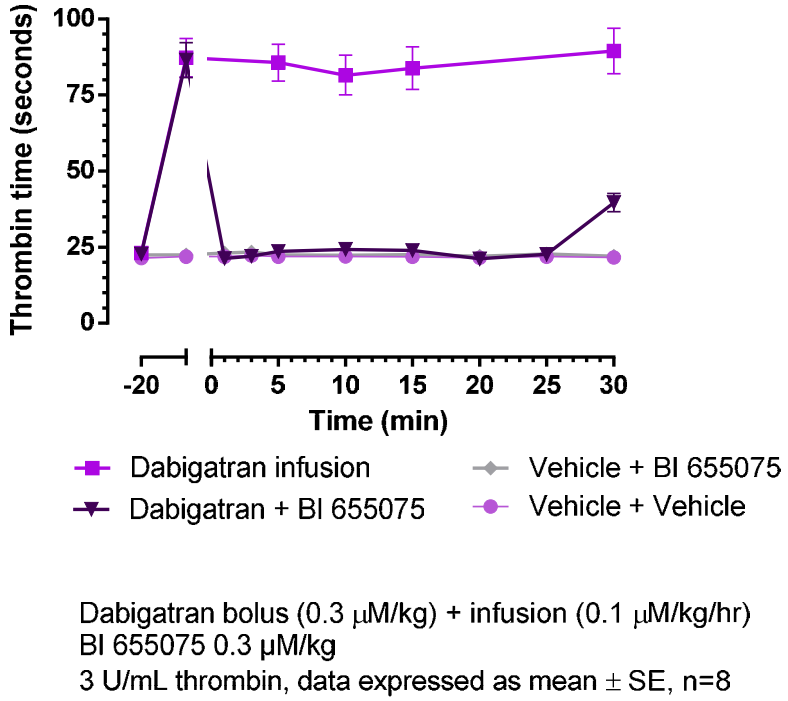



Figure 1.2: 2 The neutralization of dabigatran activity measured as thrombin time after addition of idarucizumab at t = 0. Data expressed as mean ± SE, n = 8.

Source Data: Investigator Brochure (U12-3431-02), Figure 5.1.1.5: 1A

A first-in-human trial (trial number 1321.1) [U13-1773-01] was performed according to a double-blind, randomized, single rising dose and placebo-controlled (within dose groups) design in young healthy male volunteers.

The primary objectives of the single rising dose first-in-human trial were to investigate safety, tolerability, and pharmacokinetics of single rising intravenous doses of idarucizumab (Part 1) and to explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran (Part 2).

In Part 1 (dose groups 1 to 13), 110 subjects were allocated to placebo or single doses of idarucizumab (either as long (1 h) or short (5 min) infusion). The doses of idarucizumab in dose groups 1 to 10 (long infusion) were 20 mg, 60 mg, 200 mg, 600 mg, 1200 mg, 2000 mg, 3000 mg, 4000 mg, 6000 mg, and 8000 mg; the doses of idarucizumab in dose groups 11 to 13 (short infusion) were 1000 mg, 2000 mg, and 4000 mg.

In Part 2 (dose groups 14 to 16), 35 subjects were allocated to placebo or single doses of idarucizumab as short infusion (1000 mg, 2000 mg and 4000 mg). All subjects in Part 2 were dosed to dabigatran steady state and a single dose of idarucizumab was administered around the $C_{max}$ of dabigatran following the 7th dose on day 4.

Pharmacokinetics

Plasma concentration time-profiles of idarucizumab were obtained with 1 hour infusion or 5 min infusion with or without dabigatran etexilate 220 mg bid. The pharmacokinetics were dose-linear across the range of doses. The highest exposure was achieved with infusion of 8000 mg over 1 hour. Cmax was achieved around the end of idarucizumab infusion, followed by a rapid mono- to biphasic decline in plasma concentrations. Initial half-live of idarucizumab was short ranging from gMean 0.658 to 0.906 hours. A terminal phase was detected for idarucizumab doses of 600 mg and higher. Terminal half-life (t1/2) for these doses ranged from gMean 4.54 to 8.99 hours. The key PK parameters for the three dose groups (1, 2, and 4 g idarucizumab) who received dabigatran are shown in Table 1.2: 1. They were similar to the values seen with the corresponding doses of idarucizumab alone.

The distribution volume in the steady state (Vss) after idarucizumab infusion was approximately two times the plasma volume, suggesting that the dilution space for idarucizumab was limited to approximately the blood compartment. Over the entire dose range from 20 mg to 8000 mg, the clearance of idarucizumab was approximately constant, ranging from gMean 30.0 to 53.9 mL/min.

It is assumed that a major fraction of idarucizumab was eliminated by renal catabolism. Relevant amounts of idarucizumab were detected in urine after administration of idarucizumab doses of 1000 mg or larger, with the largest amount of idarucizumab excreted in the first urine collection interval. After increasing the dose of idarucizumab infused over 5 min from 1000 mg to 4000 mg, the fraction of idarucizumab dose excreted into urine from 0-4 hours [fe0-4 (%)] increased from 10.7 to 38.9%. The increase in the fraction of dose excreted with higher idarucizumab doses suggests the saturation of catabolism/re-uptake processes in the kidney.

Table 1.2: 1 Comparison of key pharmacokinetic parameters (N, gMean and gCV [%]) of idarucizumab by treatment (dose groups 14-16, 5 min infusion)

| | 220 mg DE+ 1000 mg (N=9) | | 220 mg DE+ 2000 mg (N=9) | | 220 mg DE+ 4000 mg (N=8) | |
|---|---|---|---|---|---|---|
| | gMean | gCV [%] | gMean | gCV [%] | gMean | gCV [%] |
| $AUC_{0-\infty}$ [nmol*h/L] | 6480 | 17.1 | 16600 | 10.7 | 30900 | 14.1 |
| Cmax [nmol/L] | 5410 | 13.5 | 12500 | 21.5 | 25800 | 25.1 |
| $t_{½}$ [h] | 4.97 | 31.1 | 8.99 | 21.6 | 7.92 | 11.3 |
| $t_{½,2}$ [h] | 0.708 | 9.41 | 0.755 | 10.8 | 0.733 | 10.6 |
| $fe_{0-4}$ [%] | 8.18 | 90.6 | 26.2 | 23.4 | 40.2 | 30.5 |
| CL [mL/min] | 53.8 | 17.1 | 41.9 | 10.7 | 45.1 | 14.1 |
| $V_{ss}$ [L] | 6.30 | 22.0 | 6.90 | 29.2 | 6.37 | 21.6 |

1 initial half life

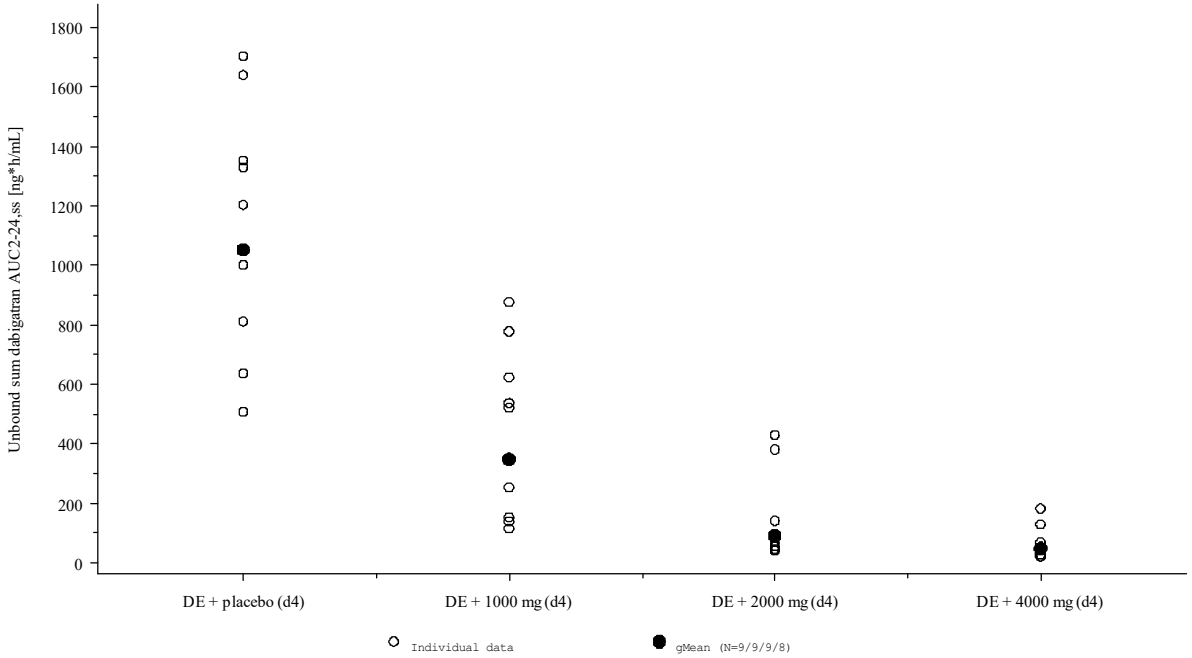
Source data: [U13-1773-01, Table 11.5.2.2.1: 2]

Binding of dabigatran and reversibility of dabigatran anticoagulant effect

In the three groups pre-treated with dabigatran etexilate, there was a rapid and substantial increase in plasma concentrations of sum dabigatran immediately after idarucizumab dosing, indicating redistribution of dabigatran into the plasma compartment due to the high binding affinity of idarucizumab to dabigatran. Importantly, the increase in sum dabigatran concentrations (also referred to as "total" dabigatran) was associated with abolished or nearly abolished anticoagulation, suggesting dabigatran was immediately neutralized through binding to idarucizumab (see Figure 1.2: 4).

The neutralizing effect was confirmed by measuring the concentration of unbound sum dabigatran before and after idarucizumab administration (see Figure 1.2: 3). “Unbound sum dabigatran” reflects the fraction of total dabigatran that is neither bound to plasma proteins nor to idarucizumab. This fraction is available to bind thrombin and thus considered pharmacologically active.

Immediately after end of idarucizumab infusion, unbound sum dabigatran concentrations were below-or close to- the lower limit of quantification in all dose groups, whereas placebo infusion had no effect on unbound sum dabigatran concentrations. The sustainability of the effect was idarucizumab dose dependent. Following administration of 2 or 4 g idarucizumab, gMean unbound sum dabigatran plasma concentrations remained below 10 ng/mL over the entire 72 hour observation period.




Source data: 1321.1: [U13-1773-01]

Figure 1.2: 3: Comparison of individual and gMean $AUC_{2\text{-}24,ss}$ values of unbound sum dabigatran after multiple oral administration of 220 mg DE bid with single iv. infusion of 1 to 4 g idarucizumab or placebo over 5 min.

Baseline measurements for the clotting parameters dTT, ECT and aPTT were taken from each subject before first dabigatran etexilate administration. A steady-state dabigatran pharmacodynamic profile was obtained after the 5th dabigatran etexilate dose. After the 7th and final dose of dabigatran etexilate (administered at time point 72 hr), sampling for clotting parameters continued for 74 h. Doses of 1, 2 or 4 g idarucizumab or placebo were administered as 5 min infusion at approximately $C_{max}$ after administration of the 7th dabigatran etexilate dose.

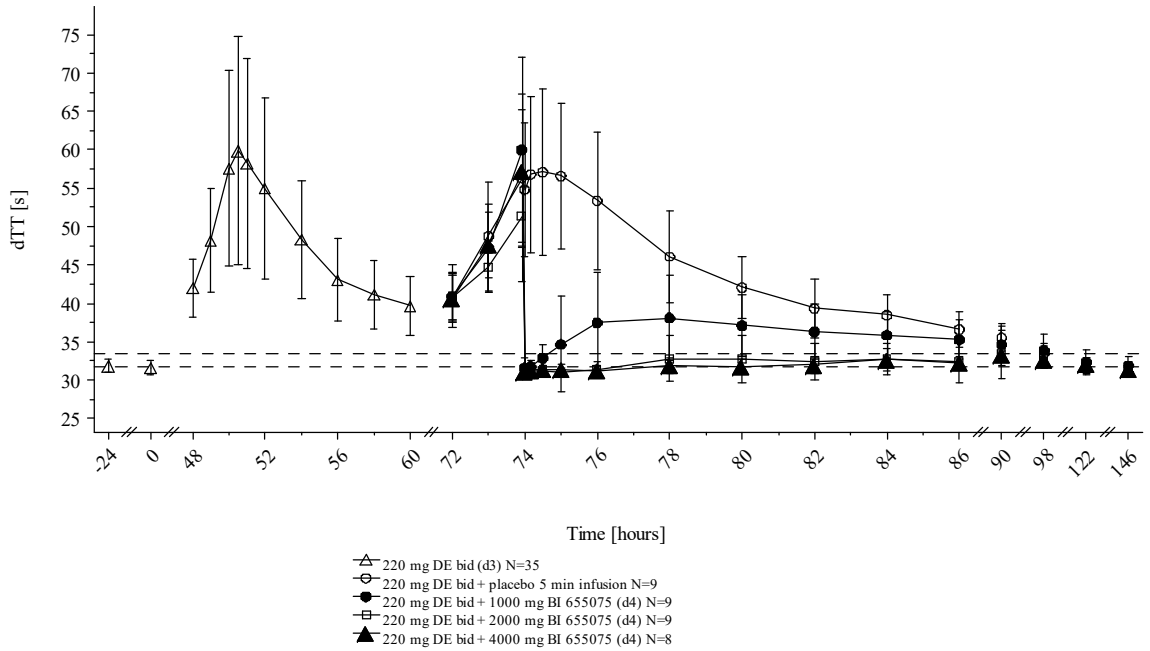
As expected, dabigatran etexilate administration in the absence of idarucizumab resulted in prolongation of clotting times as measured by all clotting parameters. At the end of idarucizumab infusion on day 4 and independent of idarucizumab dose, clotting times immediately dropped to baseline (i.e. below upper limit normal). Placebo infusion did not reverse the prolonged clotting time. The mean clotting time vs. time profiles for dTT is shown in in Figure 1.2: 3. Results with the other parameters were similar (see the idarucizumab Investigator's Brochure for additional details).

At 30 min after administration of 1000 mg idarucizumab, mean clotting times of all clotting assays increased above baseline, suggesting a partial return of dabigatran anticoagulant effect.

Following administration of 2000 mg (2 g) idarucizumab, mean dTT coagulation times remained at baseline over the entire measurement period of 72 hours. For ECT, mean

coagulation times were at or below the estimated upper limit of normal from 6 to 16 hours after end of idarucizumab infusion, with the 8 hour value being slightly above the threshold. After administration of 4000 mg (4 g) idarucizumab, mean dTT, ECT and aPTT clotting times remained at baseline over the entire measurement period.

Taken together, the results of clotting time measurements suggest that idarucizumab administration results in immediate, complete and sustained reversal of dabigatran-mediated anticoagulation.




--- Mean baseline (N=86) = 31.785 (s), normal upper reference limit (N=86) = 33.394 (s)

Source data: 1321.1: [U13-1773-01, preliminary data, report in preparation]

Figure 1.2: 4 Mean effect-time profiles (+/- SD) of dTT after multiple oral administration of 220 mg DE bid with single i.v. infusion of 1, 2, 4 g idarucizumab or placebo over 5 min at planned time 73 hours and 55 min (1 hour and 55 min after last dabigatran etexilate dose.

Target Clinical Dose

A PK/PD binding model characterizing the pharmacokinetic interaction of dabigatran and idarucizumab was developed using preclinical data and the human data from 1321.1 to assist in dose and regimen selection for subsequent trials. The calculation of the required dose of idarucizumab is based on a 1:1 stoichiometry of the binding of the Fab to dabigatran and the calculated total body load of dabigatran, reflected by the plasma concentrations and estimated volume of distribution. The dose selection also assumes that there are no dose-related safety issues (see section below on safety).

The PK data from study 1321.1 show that immediate and complete reversal of dabigatran effects could be accomplished with short intravenous infusions of the 1, 2, and 4 g doses of idarucizumab. Duration of effect was dose-dependent. Based on plasma concentration data from RE-LY patients, it was calculated that a 2 g dose of idarucizumab would neutralize the body load of a patient in RE-LY whose concentrations were at approximately the 70th percentile of the range of concentrations seen in RE-LY. That also meant that bleeding subjects with higher body loads might not achieve complete and sustained reversal with the 2 g dose. It is also known that the primary characteristics predicting bleeding in RE-LY patients are age >75 years and renal dysfunction.

Therefore a dose for reversal in bleeding patients was selected that would cover some of the highest concentrations seen in RE-LY, namely in patients with moderate renal dysfunction, most of whom are older. A dose of 5 g was calculated to cover the total body load of at least 99% of all RE-LY patients with moderate renal dysfunction, based on trough concentrations or more than 90% of these patients based on their peak concentrations.

The potential safety margin for a 10 g dose was evaluated. Idarucizumab plasma levels and exposure in preclinical studies support administration of 5 g to 10 g to humans. Compared to healthy volunteers aged 45 - 64 years that received a 5 g dose of idarucizumab, maximum plasma and exposure levels of 7-fold and 3 to 5-fold were reached in preclinical species at the No Observed Adverse Effect Level (NOAEL), based on mean Cmax and AUC0-24 levels of 25,000 nM and 37,000 nM·h reached in clinical trial 1321.2. These multiples remain unchanged if 10 g idarucizumab is administered as an initial 5 g dose followed by an additional 5 g dose greater than 24 hours later, as this regimen reflects the daily idarucizumab administration received by rats and monkeys in preclinical studies of 4- and 2-weeks duration, respectively. If idarucizumab is administered as a 10 g dose, multiples of exposure in preclinical species at the NOAEL decrease to 3-fold and 1 to 2-fold maximum plasma and exposure levels, respectively, based on estimated (modelled) human Cmax and AUC0-24 levels of 60,361 nM and 85,263 nM·h. In the event of impaired creatinine clearance (i.e., CrCL = 40 mL/min), the multiple between human maximum plasma levels and those in preclinical species decreases to 2-fold, with no effect on multiples of total exposure.

Safety in Patients

In the interim analysis of the RE-VERSE AD trial, among 90 patients followed for up to 90 days there were 18 deaths overall, with 9 in each study group; 10 deaths were due to vascular causes, including 5 fatal bleeding events. Death within 96 hours after treatment appeared to be related to the index event (2 patients had septic shock, 3 had intracranial hemorrhage, and 1 each had multiorgan failure, hemodynamic collapse, respiratory failure, and cardiac arrest), whereas all the later deaths appeared to be associated with coexisting conditions. Thrombotic events, classified as early (≤72 hours after idarucizumab administration) or late (>72 hours after administration), occurred in five patients: deep-vein thrombosis and pulmonary embolism occurred in one patient 2 days after treatment; deep-vein thrombosis, pulmonary embolism, and left atrial thrombus occurred in one patient 9 days after treatment; deep-vein thrombosis alone occurred in one patient 7 days after treatment; nonurred in one patient 7 days after treatment occurred in one patient 13 days after treatment; and ischemic

stroke occurred in one patient 26 days after treatment. None of these patients were receiving antithrombotic therapy when the events occurred. A total of 21 patients (13 patients in group A and 8 in group B) had serious adverse events during study participation. In addition to the 18 deaths and the thrombotic events that occurred in 5 patients, these events included gastrointestinal hemorrhage (in 2 patients) and postoperative wound infection, delirium, right ventricular failure, and pulmonary edema (in 1 patient each). Some patients had more than one event.

Safety in Healthy Volunteers

In part 1of study 1321.1, out of 110 subjects, 21 received placebo and 89 received single dose of idarucizumab. In subjects on treatment, 10 subjects in the placebo group (47.6%) and 32 subjects in idarucizumab group (28.5%) reported at least one AE. Out of these, 6 adverse events in 5 subjects were considered as drug related by investigator whereas only 3 of these in subjects who received idarucizumab: mild headache and erythema on the infusion site (2000 mg 1 h. Infusion), migraine (8000 mg 1 h. Infusion) and probably drawn by the study procedures.

In part 2, all 35 subjects received 7 doses of 220 mg dabigatran etexilate; then 9 received placebo and 26 received single dose of idarucizumab on day 4. A total of 27 out of 35 subjects on treatment (77.1%) in Part 2 reported at least 1 AE during the treatment period of the trial. Out of these, 6 adverse events in 5 subjects were considered as drug related whereas 4 were related to dabigatran treatment (1 epistaxis, 3 episodes of haematuria) of which 2 of these were in subjects who received idarucizumab (feeling hot and erythema at the injection site; 1000 mg group). All were of mild intensity and had resolved without sequelae at the end of the observation period. No relationship between study drug dose and incidence of drug-related AEs was observed for either part 1 or part 2 of the study.

An overview of all AEs reported during the treatment period for parts 1 and 2 is given in Appendix 10.1. Screening and post-treatment events were not included.

No deaths or other serious AEs, no protocol-specified significant AEs (i.e. events that were suggestive for cytokine release), and no AEs leading to discontinuation of the trial drug were reported in this trial.

No clinically relevant finding was reported as an AE regarding ECG recordings, physical examination, and vital sign measurements during the study. No clinically relevant changes were observed in vital signs, and main cardiac intervals (PR, RR, QRS, QT, and QTc) were unaffected. Cardiac telemetry did not reveal any abnormalities in rhythm or ST-T deviations.

With respect to laboratory parameters, there were no relevant abnormalities compared to placebo for laboratory, including clinical chemistry, haematology, coagulation parameters and urinalysis. The only remarkable finding was a dose-dependent increase in low molecular weight proteins and urine proteins observed in Part 1 and Part 2, which occurred immediately after dosing of idarucizumab and returned to normal levels within 4 to 12 h after administration of idarucizumab. The fact that these came back to normal soon after the idarucizumab administration and that there were no corresponding urine changes indicating

acute tubular injury (such as an increase in glycosuria) suggest that this phenomenon does not indicate tubular injury, but instead, reflects saturation of tubular uptake processes for the reabsorption of small (< or = ~70 kDa) proteins from the filtrate.

Anti-Drug Antibodies (idarucizumab ADA)

Of a total of 145 subjects, 19 subjects (13.1%) had positive titers at baseline (pre-dose) which tended to persist at the subsequent sampling times at end-of-study, and at 4 weeks and 3 months follow up. For placebo-treated subjects (N=36) the incidence of positive titers at baseline was 19.4% (7 of 36). For patients who received idarucizumab, 11.0% (12 of 109) had positive titers at baseline. Positive titers before administration of idarucizumab that persist at 4 weeks and 3 months follow up suggest the presence of interfering ADAs. These are thought to be pre-existing, non-specific anti-Fab antibodies, unrelated to idarucizumab.

There were no subjects on verum or placebo who developed new, persistently positive titers after treatment. Two subjects in the 60 mg dose group (Patients [redacted] and [redacted]) and one subject in the 4000 mg 5 min infusion group (patient [redacted]) were negative at pre-dose sampling but had positive titers (values of 1.0, 2.0, and 4.0, respectively) at the end of study visit. Subsequent assays in these patients at the 4 week and 3 month follow up visits were all negative.

These data indicate that in healthy volunteers, single doses of idarucizumab ranging from 20 mg to 8 g are not associated with the formation of ADAs.

Safety Conclusions

Overall, good safety and tolerability of idarucizumab administered alone up to 8000 mg 1 hour or 4000 mg 5 min infusion, and up to 4000 mg 5 min infusion at the steady state of dabigatran were observed in young healthy male volunteers. There were no notable safety findings during the trial, and no indication of a safety risk for the subjects who participated in the trial. None of the safety data presented a safety issue for further clinical trials.

For a more detailed description of the idarucizumab profile please refer to the current Investigator's Brochure (IB).

## 1.3 RATIONALE FOR PERFORMING THE TRIAL

Until recently, management of serious bleeding in patients on dabigatran etexilate, including life-threatening or fatal bleeding, consisted of supportive care, administration of blood or blood products and consideration of hemodialysis to remove the drug. A small fraction of patients who are treated with dabigatran etexilate and who have co-morbidities may require emergency surgery or other invasive procedures related to those co-morbidities, e.g. cardiac catheterization for a patient with acute coronary syndrome, surgery for a patient with acute appendicitis or major trauma without overt bleeding on presentation.

The availability of idarucizumab in many countries now allows for the use of a direct and specific reversal agent for dabigatran that is effective in the potentially life-threatening conditions described above. Until now, in China, idarucizumab has not been available. This trial is designed to confirm the therapeutic benefit of idarucizumab in Asian patient population. The reversal of the anticoagulant effects of dabigatran by idarucizumab, a monoclonal antibody fragment, has been demonstrated in volunteers and in patients (see RE-VERSE AD). This trial is designed to verify the reversibility of the dabigatran anticoagulant effect by idarucizumab in Asian patients and to support the approval of a Biologic License Application (BLA). The reversal will be demonstrated by analyzing the biomarker data in a central laboratory, independent of the clinical management of the patient. Patient outcomes will be collected and reported.

## 1.4 BENEFIT - RISK ASSESSMENT

Administration of idarucizumab to a dabigatran etexilate -treated patient reverses the anticoagulant effect of dabigatran. The data from a clinical study in patients and a Phase I study of idarucizumab clearly show that at therapeutic doses, , immediate, complete and sustained reversal of the anticoagulant effect of dabigatran is achieved. Since the pharmacologic effect of dabigatran may be a factor contributing to uncontrolled or life-threatening bleeding in some patients, the bleeding may be reduced or stopped in the presence of a specific antidote. In patients who are treated with dabigatran etexilate who are not bleeding but require emergency surgery or other invasive procedure due to other morbidities, the administration of the antidote has the potential to allow immediate intervention without risk of excessive bleeding during the surgery or procedure.

Preclinical toxicological evaluations of idarucizumab in rats and monkeys have not identified any target organ toxicity. Phase I data in 145 healthy volunteers have demonstrated the safety of single doses of idarucizumab up to a dose of 8 g. Phase III data in patients have not identified any adverse reactions. The incidence of thrombotic events is low and judged to be related to the underlying thrombotic risk in this patient population. No consistent pattern of drug-related adverse events or laboratory changes indicative of a safety issue has been observed. Potential risks to patients include possible immune reactions to the humanized antibody fragment, including anaphylaxis, neutralization of idarucizumab, formation of antibodies against dabigatran, , or lack of local tolerability or renal damage,. No hepatic impairment has been detected in patients to date. Nevertheless, hepatic toxicity has been reported for some drugs so it will be assessed in this study.

Given the positive results of the interim analysis of the RE-VERSE AD trial, i.e. the expected reversal of dabigatran effects in bleeding patients or those requiring emergency intervention, the available human safety data and the safety precautions in the study, the current benefit/risk assessment is considered to be favorable.

# 2. TRIAL OBJECTIVES AND ENDPOINTS

## 2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

### 2.1.1 Main objectives

The primary objective is to demonstrate reversal of the anticoagulant effect of dabigatran in patients treated with dabigatran etexilate who have uncontrolled or life-threatening bleeding requiring urgent intervention, and in patients treated with dabigatran etexilate who require emergency surgery or other invasive procedure.

The secondary objectives are to assess the reduction or cessation of bleeding, evaluate the clinical outcomes, safety and the pharmacokinetics of dabigatran in the presence of idarucizumab.

### 2.1.2 Primary endpoint(s)

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

### 2.1.3 Secondary endpoint(s)

**Secondary efficacy endpoints include:**

- Time to cessation of bleeding (for Group A only) since first infusion up to 24 hours after the completion of second infusion.
- Occurrence of major bleeding (for Group B only) intraoperatively and up to 24 hours post-surgery.
- Minimum unbound sum (free) dabigatran concentrations at any time point since the end of first infusion up to 4 hours after the completion of the last infusion ($C_{min,1}$).
- Reversal of anticoagulation as measured by activated partial thromboplastin time (aPTT) and thrombin time (TT), at any time point since the end of first infusion up to 4 hours after the completion of the last infusion.

**Secondary safety endpoints include:**

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

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

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

- Number of patients with immune reactions assessed by AE collection since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion

- Number of patients with thrombotic events (ischemic stroke, myocardial infarction, pulmonary embolism, deep vein thrombosis, systemic embolism) since the first infusion up to 5 days after the completion of the second infusion and since informed consent up to 30 days (±7 days) after the completion of the second infusion

**Further safety endpoints**

- Clinically relevant changes in laboratory parameters, including renal and hepatic function
- Blood pressure and heart rate hourly while in emergency department and every 4 hours for the next 72 hours

# 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

## 3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will be an open-label, multicenter, multinational study, with a single treatment arm, idarucizumab. The target population will be patients who have been treated with dabigatran etexilate who either have uncontrolled bleeding requiring medical intervention, or who need emergency surgery or a procedure for a condition other than bleeding where therapeutic anticoagulation would, in the opinion of the treating clinician, unduly increase the risk of intra- and post-operative bleeding.

There are two separate but related elements in this study, the pharmacologic reversal of dabigatran and the clinical management of the patients. The biomarker tests to demonstrate reversal will be done in a central laboratory, temporally and geographically separated from the sites managing patients. The investigator will make clinical decisions dependent only on the status of the patient and any local tests or lab parameters, including local clotting tests if available, e.g. aPTT. Dosing of idarucizumab will not be affected by a local lab test. The investigator may or may not see rapid resolution of bleeding, or adequate control of bleeding during surgery, depending on the patient and the elements contributing to the bleed. It is important to understand that the selection of patients, the dose of antidote and the management of the patients are not dependent on the measurement of dabigatran reversal. Analyses of correlations between the reversal effect and clinical outcomes will be undertaken after completion of the trial.

The patients may be identified in ambulances or the Emergency Department or similar department of participating hospitals. After determination that the patient has been treated with dabigatran etexilate, the informed consent process will occur. Due to the need for urgent care in these patients, collection of medical history and other standard of care information (e.g. laboratory values, vital signs, weight, ECG) up to the time of consenting may be collected on the CRF.

The determination of whether the patient is being treated with dabigatran etexilate will be based on information provided by the patient, by a patient representative (family member/relative), or the patient's physician. Baseline (pre-dose) blood samples for PK/PD measurements will be taken in all patients. After the pre-dose samples are taken, idarucizumab will be administered. All patients will receive 5 g of idarucizumab, administered as two separate infusions of 2.5 g, no more than 15 minutes apart. In rare instances, an additional 5 g dose is justified (see Section 4.1.2). Further blood sampling will occur just prior to the second 2.5g infusion, between 10 and 30 minutes after the second infusion and 1, 2, 4, 12, 24 hours and 30 days after the second dose. Actual sampling time will be recorded. The patient will be monitored for bleeding, adverse events and clinical status throughout the study. The duration of the study for each patient is 30 days. In the first 24 hours, approximately 137 ml of blood will be taken depending on available tube size. A total of approximately 140 mL of blood will be taken during the study overall, depending on available tube size. If a patient requires an additional 5 g dose of idarucizumab, approximately 137 mL (baseline to 24 hours) of additional blood may be drawn.

## 3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A trial in healthy male volunteers receiving dabigatran etexilate has demonstrated the reversal of dabigatran effects compared to placebo (study number 1321.1). A study in patients has also demonstrated safety and efficacy (study number 1321.3). The current trial is designed to verify the previously observed reversal of the anticoagulant effects of dabigatran in patients that received dabigatran etexilate and have uncontrolled bleeding or require emergency surgery or invasive procedures, as well as to track the clinical course and outcomes of the patients. Thus, each patient will have an assessment of pre-treatment coagulation status and clinical status (baseline) followed by post-treatment measurements to determine the extent of reversal of dabigatran and the clinical course of the patient. By providing baseline and post-treatment clotting assessments, each patient acts as his own control. Demonstration of reversal of dabigatran effects in patients via central lab measurements is the primary goal, although this information will not be available to the treating physician at the time of the bleed or surgery. Clinical endpoints such as patient status, whether the bleeding stops or diminishes may vary widely depending on the clinical situation so these will be secondary endpoints. In addition, patients treated for dabigatran-associated intracranial hemorrhage (ICH) will be analyzed separately, as treatment options and prognoses are very different for these patients than for those with hemorrhage elsewhere in the body. Accordingly, for the ICH cohort, a modified Rankin Score (mRS) assessment will be performed on Day 1 and Day 7 follow-up (or the date of hospital discharge if the patient discharge before Day 7). In addition, where available, comparisons of sequential CT scans of ICH patients performed as part of the standard of care at the institution will be done to estimate blood volumes.

Recruitment of patients is challenging. The frequency and timing of bleeding or emergency surgery in dabigatran etexilate -treated patients cannot be predicted in advance. Where the patient will be treated for the bleeding is also difficult to predict. With major bleeding events that require hospitalization occurring at a rate of 2-3 events per 100 patient-years of dabigatran etexilate treatment, these factors mean that even large community or academic hospitals treat only a handful of patients a year, at most. Furthermore, for a variety of clinical reasons, some patients may be treated with intensive support and red blood cell transfusion instead of actual reversal of anticoagulation. For these reasons, this trial will include approximately 30 hospitals. We anticipate approximately 2 years will be required to recruit the target number of patients.

The bleeding cases eligible for this study require urgent intervention and will be life-threatening in some cases. Fatal bleeds have occurred. Supportive care alone may not be sufficient to stop the bleeding. Therefore the inclusion of a control group (supportive care without the antidote) is regarded as unethical and so all patients will receive the antidote in an open-label manner. It may require only a relatively small number of cases to demonstrate that reversibility is achieved.

The trial will include a single arm consisting of a fixed dose of idarucizumab calculated to achieve reversal in at least 99% of patients. There are no widely available tests to determine

whether a smaller dose might suffice in some patients, so different doses will not be compared.

## 3.3 SELECTION OF TRIAL POPULATION

This trial will be conducted as a multicenter, multinational trial in Asian patients with duration of approximately 2 years. It is expected approximately 30 sites will participate in this study. The recruitment of patients who meet the inclusion/exclusion criteria is expected to be slow with an average rate of less than 1 patient per site per year. There is no upper age limit for the study. The average age of patients in the RE-LY study was 71 years old. Forty percent of RE-LY patients were 75 years old or greater.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated with investigational drug or not.

### 3.3.1 Main diagnosis for trial entry

There are two separate groups of patients with different diagnoses:

**Group A.** Patients who are taking dabigatran etexilate and have uncontrolled or life-threatening bleeding requiring urgent medical or surgical intervention

**Group B.** Patients who are taking dabigatran etexilate who may not be bleeding, but do require an emergency surgery or other invasive procedure for a condition other than bleeding, where therapeutic anticoagulation with dabigatran etexilate is undesirable

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

### 3.3.2 Inclusion criteria

1. ≥ 18 years at screening.

2. Male or female patients. Women of childbearing potential (WOCBP)[1] and men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

3. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

4. Currently taking dabigatran etexilate

5. They meet the following criteria:

**Group A:** Overt bleeding judged by the physician to require a reversal agent.

**OR**

**Group B:** A condition requiring emergency surgery or invasive procedure where adequate hemostasis is required. Emergency is defined as within the following 8 hours.

### 3.3.3 Exclusion criteria

**Group A:**

1. Patients with minor bleeding (e.g. epistaxis, hematuria) who can be managed with standard supportive care.

2. Patients with no clinical signs of bleeding.

3. Contraindications to study medication including known hypersensitivity to the drug or its excipients (subjects with hereditary fructose intolerance may react to sorbitol).

**Group B:**

1. A surgery or procedure which is elective or where the risk of uncontrolled or unmanageable bleeding is low.

2. Contraindications to study medication including known hypersensitivity to the drug or its excipients (subjects with hereditary fructose intolerance may react to sorbitol).

### 3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the treated patients in the trial: if possible on tretament, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures during inform consent, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF.

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart (FC) and section 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

Categorization of withdrawal is as follows:

1. Patient discontinues treatment but completes protocol procedures-Patient refuses to receive all study medication but completes all of the protocol specified procedures.
2. Patient discontinues treatment but has some protocol procedures-Patient refuses to receive all the study medication but completes some of the protocol specified procedures.
3. Patient discontinues treatment and does not want to complete any protocol procedures-Patient refuses to receive all the study medication and does not want to complete any of the protocol specified procedures, but is willing to be followed with phone calls.
4. Patient discontinues treatment and does not want to be contacted at all-Patient refuses to receive all the study medication and does not want to complete any of the protocol specified procedures, does not want any type of contact at all (consent withdrawn).

Once a patient receives study medication, all observations outlined in the protocol should be performed. If a patient withdraws after receiving study medication, the last study visit

should be performed and the information recorded in the eCRFs. All available data from patients who discontinued during the trial, for whatever reason, will be included in the analysis. Early discontinuations must be reported to the sponsor.

Completion of treatment is defined as patients who have received 5g (or 10 g if applicable) of study medication and have at least one post study drug blood sample. Completion of the study is defined as patients who complete all study visits.

#### 3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see section 3.3.4.1 above.

#### 3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

# 4. TREATMENTS

## 4.1 INVESTIGATIONAL TREATMENTS

The sole treatment for administration in this trial is idarucizumab, a humanized monoclonal antibody fragment (Fab), administered as an intravenous infusion. There is no comparator treatment.

### 4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1:

| | |
|---|---|
| Substance: | Idarucizumab (BI 655075) |
| Pharmaceutical formulation: | Intravenous solution |
| Source: | Boehringer Ingelheim |
| Unit strength: | 2.5g per vial |
| Posology | 5.0g (in rare instances an additional 5 g dose is justified. See Section 4.1.2) |
| Route of administration: | Intravenous |

Idarucizumab drug product (50mg/ml) is formulated as a buffered, isotonic, preservative-free solution of idarucizumab in a buffer consisting of 22 mM sodium acetate, 220 mM Sorbitol, 0.2 g/L (0.02w%) Polysorbate 20 and water for injection. Idarucizumab is a colorless to slightly yellow, clear to slightly opalescent solution, with an osmolality of 27-330 mOsm/kg and a pH of 5.3-5.7.

### 4.1.2 Selection of doses in the trial

The dose is 5.0g, administered as two separate 2.5g vials given no more than 15 minutes apart. As described in Section 1.2 under *Target Clinical Dose*, a dose of 5 g of idarucizumab is calculated to completely reverse the effect of dabigatran in at least 99% of patients. The full 5 g must be administered to all patients and the treating physician may give the second infusion as soon as judged necessary after the first dose but no later than 15 minutes after completion of the infusion the first dose. In rare instances during the same hospitalization, after the initial 5 g dose, a patient may experience a re-start of bleeding or have a potential for a life-threatening bleed or have a need for an additional emergency surgery/procedure, coupled with re-elevation of local clotting tests. In such cases, an additional 5 g dose is justified.

### 4.1.3 Method of assigning patients to treatment groups

There is only one treatment group in this study. If applicable, the pharmacist or designee will dispense the study medication.

### 4.1.4 Drug assignment and administration of doses for each patient

Drug dispensing may occur via the hospital pharmacy, a secure storage location in the Emergency Department, or other secure location such as the blood bank. Each 50 ml vial contains 2.5g of idarucizumab. For both Group A and Group B, the first vial of the drug should be administered as a rapid IV infusion with (in order of preference, a 5 min infusion with an infusion pump, a 10-15 min drip, or iv push with a syringe followed by a second vial of 2.5g idarucizumab no later than 15 minutes after the end of the first dose. The infusion/injection may be filtered using an in-line 0.2 μm filter. The infusion of each vial should take no longer than 5-10 minutes.

### 4.1.5 Blinding and procedures for unblinding

#### 4.1.5.1 Blinding

Not applicable. There's only one treatment arm in this open-label study.

#### 4.1.5.2 Unblinding and breaking the code

Not applicable.

### 4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

For details of packaging and the description of the label, refer to the ISF.

### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

### 4.1.8 Drug accountability

The investigator or pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee ,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

The investigator < and/or > pharmacist < and/or > investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational product and trial patients. The investigator / pharmacist / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor< and/or >appointed CRO, the investigator / pharmacist / investigational drug storage manager must verify that all unused drug supplies have been returned by the clinical trial investigators and that no remaining supplies are in the investigator's possession.

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

For patients who continue to bleed, supportive care with blood products such as fresh frozen plasma, fresh or packed red blood cells (RBCs), or packed platelets are permitted. Administration of activated prothrombin complex concentrates (PCCs, e.g. FEIBA) or recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X may be considered, even though their use has not been evaluated in clinical trials. Dabigatran can be hemodialysed out of the patient's circulation. Approximately 60% of the drug can be removed over 2-3 hours (P13-01830), (P13-04186).

### 4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Prior treatment with the dabigatran antidote carries a theoretical risk of anti-idarucizumab antibody formation, a possible immune reaction to the antidote and possible diminution of the efficacy of the antidote.

Administration of dabigatran etexilate to a bleeding patient or a patient requiring emergency surgery should be interrupted. There are no known restrictions on other drugs at this time.

Some active idarucizumab may remain circulating for up to 24 hours after infusion (less than 1% of the dose in subjects with normal renal function, but somewhat more in subjects with renal insufficiency or failure). This may impact the expected efficacy of re-instituted anticoagulation with dabigatran etexilate. Re-anticoagulation with any agent should only be considered after the patient who has experienced major bleeding or surgery is deemed clinically stable and adequate hemostasis has been achieved. If there is an urgent indication to re-start anticoagulation after study treatment, the clinician must evaluate the risk-benefit ratio of doing so in the specific patient. The clinician may then choose to give one or more doses of a parenteral antithrombotic such as low molecular weight heparin as a bridging therapy prior to re-initiation of dabigatran etexilate. In patients with creatinine clearance <30 mL/min dabigatran etexilate should not be re-started until the renal function has been corrected, or a longer term alternative anticoagulant should be chosen. Re-institution of anticoagulation is not a requirement of this trial, but is left to the discretion of the treating physician.

4.2.2.2 Restrictions on diet and life style

Not applicable.

#### 4.2.2.3 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described in the patient information.

## 4.3 TREATMENT COMPLIANCE

The study drug is administered as an intravenous infusion. The administration start and stop times of the first and second infusions will be recorded. Any interruptions or discontinuations of infusions will also be recorded. See Section 4.1.4 for method of administration.

# 5. ASSESSMENTS

## 5.1 ASSESSMENT OF EFFICACY

Efficacy will be based on central laboratory determination of reversal of the anticoagulant effect of dabigatran, using several coagulation tests [thrombin time (TT), diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and local assessment of aPTT. aPTT will be measured both locally and centrally.

Reversal of anticoagulant effect will be characterized by the maximum reversal achieved for each patient, the time to maximum reversal and the duration of reversal. The proportion of patients achieving at least 100% reversal will also be calculated. No dosing or patient management decisions are based on central lab determination of reversal. Dosing of idarucizumab will not be affected by a local lab test. Maximum reversal of the anticoagulant effect of dabigatran is defined as

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

Values equal to or higher than 100% will be interpreted as complete reversal of the anticoagulant effect.

The ULN will be determined using data from 1321.1 and 1321.2. It will be calculated as the (arithmetic) mean + 2*SD using all data collected prior to the dosing of dabigatran and the data from subjects who were on placebo as well as pre-dose data from idarucizumab alone treatment (as available), SD denotes the standard deviation.

## 5.2 ASSESSMENT OF SAFETY

### 5.2.1 Physical examination

A physical examination will be performed at the time points specified in the flowchart. It includes height and body weight.

The results must be included in the source documents available at the site.

### 5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.

This includes systolic and diastolic blood pressure, temperature and heart rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest.

### 5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed include hematology, chemistry, aPTT and any applicable local lab testing to facilitate patient clinical management. For the sampling time points please see the flowchart.

All analyses will be performed by local laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

### 5.2.4 Electrocardiogram

Electrocardiograms (ECG) will be performed at baseline and on day seven (Visit 4) of the study. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

### 5.2.5 Other safety parameters

Not applicable

### 5.2.6 Assessment of adverse events

#### 5.2.6.1 Definitions of AEs

**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 to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including 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.

**Serious adverse event**

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

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.

AEs Considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and AE reporting to sponsor and timelines"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

**Adverse events of special interest (AESIs)**

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 trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see above.

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC system.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

**Intensity (severity) of AEs**

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Sufficient discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

**Causal relationship of AEs**

Medical judgement 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 that there is a reasonable possibility of a 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 aetiologies that could explain the event (e.g. pre-existing 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 trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

**AE Collection**

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

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial:
  - all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:

the investigator does not need to actively monitor the patient for AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

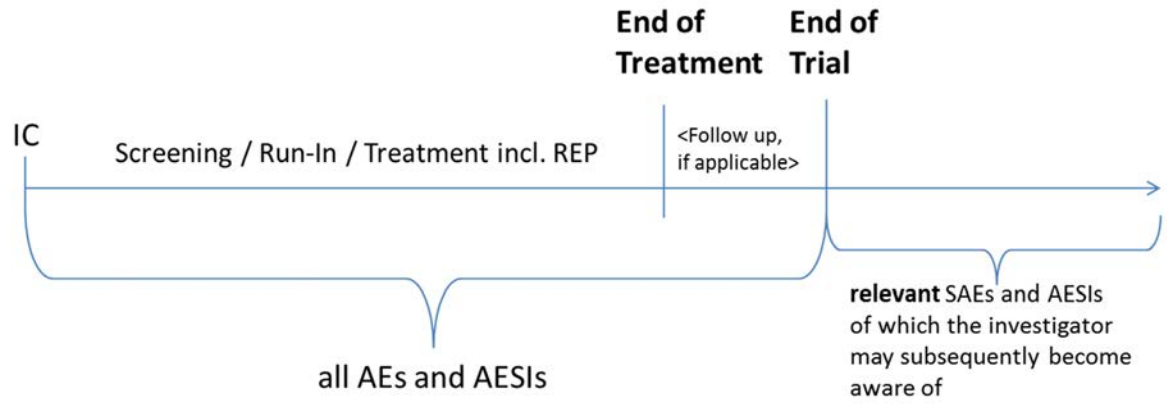



Figure 5.2.6.2: 1 AE and AESIs report

**AE reporting to sponsor and timelines**

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours ) to the

sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

**Information required**

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

The following should also be recorded as an (S)AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

**Pregnancy**

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies and not the SAE form is to be

completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

## 5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

### 5.3.1 Assessment of pharmacokinetics

For pharmacokinetic endpoints that are determined as secondary endpoints and further endpoints, refer to Section 2.1.3 and 2.2.2.

### 5.3.2 Methods of sample collection

5.3.2.1 Pharmacokinetic, anti-drug antibody, and biomarker assays

A total amount of approximately 105 mL blood will be taken per patient during the course of the study for central lab assessment of pharmacokinetic, anti-drug antibody and biomarker purposes. In addition, approximately 35mL of blood will be drawn for local aPTT and safety lab assessments.

Blood collection supplies for central lab measurements will be provided.

K-EDTA and/or Na Citrate blood samples will be collected at time points specified in the Flow Chart and as summarized in Table 5.3.2.1: 1 below in order to prepare plasma for use in the following assays:

Pharmacokinetic (PK) assays:

1. idarucizumab
2. dabigatran (as specified below)

    - "sum" dabigatran = total amount of dabigatran in plasma (after sample hydrolysis, i.e. comprising the sum of unconjugated plus glucuronide conjugated dabigatran)

    - "unbound sum" dabigatran = fraction of "sum" dabigatran (after plasma ultrafiltration, i.e. the sum of unconjugated plus glucuronide conjugated dabigatran, that is neither bound to idarucizumab nor to plasma proteins)

[redacted]

Biomarker assays:

1. Ecarin Clotting Time (ECT)
2. diluted Thrombin Time (dTT)
3. activated Partial Thromboplastin Time (aPTT)
4. Thrombin Time (TT)

For assays, blood will be collected from a forearm vein in a blood drawing tube with the appropriate anticoagulant at time points indicated in the Flow Chart and in Table 5.3.2.1: 1. For a complete list of central and local blood draws, see Appendix 10.2. If it is not possible to obtain venous blood, blood can be collected from an arterial access. Whether the blood collection is venous or arterial should be documented in the e-CRF.

Table 5.3.2.1: 1 Summary of blood sampling schedule (approximate volumes)[@]

| | K-EDTA blood | | Na-citrate blood | |
|---|---|---|---|---|
| Analytes →<br><br>Timepoint ↓ | PK assays (1 & 2) | Total volume* | Biomarker assays (1-4) | Total volume* |
| Baseline | X | 12 mL | X | 4.5 mL |
| Vial #1 (no blood) | | | | |
| just prior to vial 2 | X | 6 mL | X | 4.5 mL |
| Vial #2 (no blood) | | | | |
| between 10-30min | X | 6 mL | X | 4.5 mL |
| 60min +/- 15 min | X | 6 mL | X | 4.5 mL |
| 2hour +/- 30 min | X | 6 mL | X | 4.5 mL |
| 4hour +/- 30 min | X | 6 mL | X | 4.5 mL |
| 12hour +/- 1 hour | X | 6 mL | X | 4.5 mL |
| 24hour +/- 2 hour | X | 6 mL | X | 4.5 mL |
| Day 30 | | 3 mL | | |

*Sample volumes may vary depending on the availability of sample collection tubes, therefore the indicated blood volumes per sampling time point are approximate and actual volumes may differ slightly. The total volumes as indicated in 5.3.2.1 will not be exceeded.

[@] **If a patient requires an additional 5 g dose of idarucizumab see Section 10.2 for additional details.**

Actual clock times must be recorded for every sample. For the early time points after drug administration, samples should be obtained from the forearm not used in the idarucizumab infusion. If this is not possible an appropriate volume of blood should be voided prior to sampling. Start the blood sampling with K-EDTA collection tubes followed by Na-Citrate tubes. Immediately after blood sampling, the drawing tubes should be gently inverted 10 times and transferred into an ice water bath for temporary storage until centrifugation.

Centrifugation will be done within 30 minutes after sample collection. Plasma will be transferred to new appropriately-labelled polypropylene tubes and stored in an upright position at about -20°C or below. Plasma samples should be shipped to the central lab within 1 week.

For clear identification of the samples, the sample labels should be completed carefully with the required information.

For further details on sample handling and shipment, refer to ISF chapter 10 / lab manual.

Validated methods will be used for all analytes. Analyses will be conducted at laboratories specified in Section 5.3.3 and Section 5.4.2. The sponsor may appoint other laboratories for method development and sample analysis, if necessary.

After completion of the study, the plasma samples obtained for pharmacokinetic and anti-drug antibody assays may be used for further methodological investigations, e.g., for stability testing. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

Unused samples for biomarker analysis may be used for coagulation assay development and validation purposes, e.g., method comparison or sample stability studies. These analyses may be performed in laboratories [redacted], if necessary. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

[redacted]

### 5.3.4 Pharmacokinetic – pharmacodynamic relationship

Refer to section 7.3.5

## 5.4 ASSESSMENT OF BIOMARKER(S)

### 5.4.1 Endpoints based on biomarkers

Biomarker endpoints are the basis for determination of efficacy in this trial. Some biomarkers may be only for investigational use, for example, the dTT assay is investigational in USA.

Ecarin clotting time (ECT), diluted Thrombin Time (dTT), activated Partial Thromboplastin Time (aPTT) and Thrombin Time (TT) will be measured in a central laboratory.

For biomarker endpoints that are determined as primary or secondary endpoints refer to Section 2.1. Further endpoints based on biomarkers include:

For ECT, dTT, aPTT and TT as feasible:

- $E_{pre}$ (value of the biomarker assay determined in a plasma sample prior to administration of idarucizumab)
- $E_{pre,1}$ (value of the biomarker assay determined in a plasma sample after the first, but prior to the second administration of idarucizumab)

[redacted]

## 5.5 OTHER ASSESSMENTS

Investigators may also draw blood for routine laboratory parameters according to the standard of care to evaluate the patient's clinical status and manage patient care. In addition, investigators may also evaluate vital signs, hemodynamics and other parameters as part of patient management and stabilization. These parameters, (blood pressure, heart rate, hematology, hemodynamics) will be used to determine clinical status of the patient.

Bleeding severity for the index bleed (Group A) or any unusual bleed associated with surgery (Group B) will be assessed at baseline by the treating clinician and where possible will be classified according to three different scales: major or life-threatening bleeding (ISTH definition), and the TIMI and GUSTO classifications [ISTH: International Society for Thrombosis and Hemostasis, GUSTO: Global Strategies for Opening Occluded Coronary Arteries, TIMI: Thrombolysis In Myocardial Infarction]. For ICH patients with serial CT scans performed as standard of care at baseline and e.g. 24 hours, an estimate of changes in intracranial blood volume will be made. and sites will be requested to submit de-identified

copies of the scans for review by the EAC. Glasgow Coma Scale and Modified Rankin Scale will also be assessed for ICH patients.

Baseline assessment:

- Overt bleeding that, in the opinion of the treating physician is severe, ongoing, possibly related to dabigatran etexilate use, and requires reversal of the anticoagulant effect

In cases where haemoglobin or haematocrit values are not available for Group A patients during the conduct of the study then bleeding scales may be assessed retrospectively based on data associated with the 1 hour, 2 hours, 4 hours, 6 hours, 12 hours and 24 hours post dose time points.

ISTH Bleeding Classification

Major bleeding must satisfy one or more of the following criteria:

- Overt bleeding associated with a reduction in hemoglobin of at least 2 g/dL or leading to a transfusion of at least 2 units of blood or packed cells

- Symptomatic bleeding in a critical area or organ: intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal, intra-articular or pericardial bleeding

Major bleeding is classified as life-threatening if one or more of the following criteria are met:

- Fatal bleeding, symptomatic intracranial bleeding, a reduction in hemoglobin of at least 5 g/dL, transfusion of at least 4 units of blood or packed cells, bleeding associated with hypotension requiring use of intravenous inotropic agents, or bleeding necessitating surgical intervention.

TIMI Bleeding Classification

Major Intracranial hemorrhage or a ≥5 g/dL decrease in the hemoglobin concentration or a ≥15% absolute decrease in the hematocrit

Minor Observed blood loss: ≥3 g/dL decrease in the hemoglobin concentration or ≥10% decrease in the hematocrit

No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration or ≥12% decrease in the hematocrit

Minimal Any clinically overt sign of hemorrhage (including imaging) that is associated with a <3 g/dL decrease in the hemoglobin concentration or _<9% decrease in the hematocrit

*All TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dL or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between two blood measurements is calculated as follows:
Δ Hemoglobin =_ [baseline Hgb - post-transfusion Hgb] + [number of transfused units];
Δ_ Hematocrit _ [baseline Hct - post-transfusion Hct] + [number of transfused units x 3].

GUSTO Bleeding Classification

Severe or life-threatening Either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention

Moderate Bleeding that requires blood transfusion but does not result in hemodynamic compromise

Mild Bleeding that does not meet criteria for either severe or moderate bleeding

Glasgow Coma Scale and Modified Rankin Scale

Patients with intracranial hemorrhage will be assessed by the Glasgow Coma Scale and, at final follow-up, Modified Rankin Scale (see Appendix 10.4)

## 5.6 APPROPRIATENESS OF MEASUREMENTS

The choice of central lab measurement of coagulation tests dTT or ECT as the primary endpoint was explained in Section 3.2. Clinical outcomes such as bleeding reduction, bleeding cessation, [redacted] and clinical status of the patient (including [redacted] for ICH patients, mRS at 30 days) will be recorded as secondary endpoints.

The use of the coagulation tests, thrombin time (TT), diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT) are standard tests used in the evaluation of a medication with this mechanism of action. It cannot be excluded that co-medications such as volume expanders affect the accuracy of these parameters. In case of dTT, the plasma sample is 8 fold diluted with standardized plasma prior to measurement, ensuring that the effect is minimal. Preclinical data show little impact of plasma expanders on the reversal with idarucizumab; animal studies of PCCs show some improvement in bleeding. As these coagulation markers are widely used in clinical practice, potential effects need to be considered. Nevertheless we will carefully tabulate the use of these concomitant therapies.

Non-standard tests such as dabigatran levels, anti idarucizumab antibody levels will be evaluated to fully elucidate the action of the study medication and determine the ability of idarucizumab to be effective for subsequent uses in the same patient.

# 6. NVESTIGATIONAL PLAN

## 6.1 VISIT SCHEDULE

A summary of scheduled assessments for the study is presented in the Flow Chart. The study data will be collected at the time of the visit and by medical record review.

During the screening visit at any time of day or night, eligible patients receiving dabigatran etexilate who are exhibiting signs and symptoms of uncontrolled bleeding requiring urgent medical intervention, or who require emergency surgery or other medical procedure requiring rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure may be asked to participate.

Eligible patients will receive study medication after meeting inclusion and exclusion criteria. All patients who receive study medication will be followed up for 30 days.

A patient visit may be rescheduled as long as it is within the acceptable time windows of the protocol. Every effort should be made to have the patient adhere to the visit schedule. Patients who prematurely withdrawn from study medication must undergo end-of-study (Visit 5) procedures.

## 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

### 6.2.1 Screening and run-in period(s)

Visit 1 (Day 1): Screening Period (Baseline)

When a patient presents to the investigative team, gives consent, meets all inclusion/exclusion criteria and it is confirmed that the patient has been taking dabigatran etexilate, the patient will be eligible to participate in the study. Due to the need for urgent care in these patients, collection of medical history and other standard of care information (e.g. laboratory values, vital signs, weight, ECG) up to the time of consenting may be collected on the CRF.

After obtaining informed consent for the study the following procedures will be performed:

- Bleeding or surgery/procedure assessment
- Perform spot urine or other appropriate pregnancy test if applicable. Recruitment of pregnant patients is allowed only after a careful evaluation/discussion of the risks and benefits of study participation between the treating physician and patient, unless it is against local regulations.
- Baseline blood draw for central biomarker, PK and local lab safety evaluation
- ECG

- Glasgow Coma Scale (GCS) and Modified Rankin Score (mRS) if ICH cohort
- Record concomitant therapy
- Record adverse events
- Record demographics, medical history and physical examination (including height, weight and temperature)
    - Complete medical records do not need to be available prior to study entry. A verbal medical history can be used to verify that the patient meets all of the inclusion and none of the exclusion criteria, but must be verified using medical records following enrolment in the study. Three documented attempts (2 phone calls and 1 written) must be made to obtain medical records. If unable to obtain the medical records the study coordinator must contact the CML.

### 6.2.2 Treatment period(s)

Study medication will consist of two vials of 2.5g idarucizumab (total dose 5.0g) administered no longer than 15 minutes apart. In most cases, patients will sign the consent form and receive study medication on the same day.

**Visit 2.1 (Day 1 continued):**

Observations and Procedures:

- Administer first vial (2.5g) of study medication. Record start and stop time of administration
- Bleeding or surgery/procedure assessments
- Measure blood pressure and heart rate hourly while the patient is in the emergency department (or similar department), then every 4 hours for the next 72 hours or until patient is discharged
- Record adverse events
- Record concomitant therapies

**Visit 2.2 (Day 1 continued):**

Observations and Procedures:

- Draw blood for both central and local laboratories just prior to the infusion of second vial of study medication. Record time of blood draw
- Administer second vial (2.5g) of study medication no later than 15 minutes after the completion of the first vial. Record start and stop time of administration
- Draw blood for both central and local laboratories between 10 and 30 minutes, and 1, 2, 4 and 12 hours after the second vial of study medication. Record times of blood draws
- Bleeding or surgery/procedure assessments at or near times of blood draws

- Measure blood pressure and heart rate hourly while the patient is in the emergency department (or similar department), then every 4 hours for the next 72 hours or until patient is discharged.
- Record adverse events
- Record concomitant therapies
- In rare instances during the same hospitalization, e.g. 2 to 24 h after the initial 5 g dose, a patient may experience a re-start of bleeding or have a potential for a life-threatening bleed or have a need for an additional emergency surgery/procedure, coupled with re-elevation of local clotting tests. In such cases an additional 5 g dose is justified and the patient should be allocated a new patient number. Blood sampling times are the same as with the first 5 g dose or as logistics permit (Prior to administration of the third vial, just prior to the fourth vial, as well as between 10 and 30 min, 1, 2, 4, 12, 24 hours, and 30 days after the end of the infusion of the fourth vial). Other study procedures and tests should be performed per protocol.
- Perform study drug accountability

### 6.2.3 Follow up period and trial completion

**Visit 3 (24-hour after completion of the second vial ± 2 hours)**
Observations and procedures

- Draw blood for both central and local laboratories for patients while in the cardiac cath lab 24 hours after the end of the second vial of study medication. Record time of blood draw.
- Bleeding or surgery/procedure assessments
- Measure blood pressure and heart rate hourly while the patient is in the emergency department (or similar department), then every 4 hours for the next 72 hours or until patient is discharged.
- Record adverse events
- Record concomitant therapies
- Re-start appropriate anticoagulant therapy (investigator discretion)

**Visit 4 (7 days +/- 3 days after the second vial)**
Observations and procedures

- Bleeding or surgery/procedure assessment
- Measure blood pressure and heart rate hourly while the patient is in the emergency department (or similar department), then every 4 hours for the next 72 hours or until patient is discharged
- ECG
- Modified Rankin Score (mRS) if ICH cohort
- Record adverse events
- Record concomitant therapies

**Visit 5 (End of Study, 30 days +/- 7 days after the second vial)**
Observations and procedures

- Bleeding or surgery/procedure assessment

- Measure blood pressure and heart rate
- Draw blood for central laboratories
- Perform urine or other appropriate pregnancy test if applicable
- Record adverse events
- Record concomitant therapies
- Modified Rankin Score (mRS) if ICH cohort
- Conclusion of patient participation

# 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

## 7.1 STATISTICAL DESIGN - MODEL

This trial has a single treatment group with no control group. It is a case series with reversal of anticoagulation effect in each patient determined by pharmacodynamic parameters (Section 5.1). There is no statistical model for this trial. Assessment of efficacy will be based on descriptive statistics, with confidence limits provided when appropriate.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no hypothesis testing for this trial.

## 7.3 PLANNED ANALYSES

Safety summaries will be based on all patients who have received at least one vial of idarucizumab. The primary analysis will include patients who have received any idarucizumab and have a pre-dose and at least one PD measurement within 4 hours after the administration of the 2nd vial of idarucizumab. Other efficacy analyses will include patients who have received one or two vials of idarucizumab and have pre-dose and at least one post-dose PD measurement. Therefore the number of patients included in the efficacy analysis may be different for different endpoints.

Efficacy endpoints are defined in Section 2.1. Analysis of efficacy and safety endpoints will be descriptive in nature. The efficacy analysis for reversal will also exclude patients with a pre-dose coagulation test value below 100% ULN.

### 7.3.1 Primary endpoint analyses

For the primary endpoint, the median and other quantiles of the calculated reversal of the anticoagulation effect will be summarized.

### 7.3.2 Secondary endpoint analyses

For secondary efficacy endpoints, the following analyses are planned:

- For cessation of bleeding (for Group A only): the time to cessation of bleeding will be summarized using descriptive statistics, such as, median, or proportions as appropriate, by type of bleedings. Bleeding status will be categorized before and at several time points after treatment. For ICH patients, this will depend on availability of follow up CT

scans. ICH patients will not be included in this analysis if no regular follow-up CT scans are available.

- The occurrence of major bleeding (for Group B only) will be summarized descriptively. Frequency, proportions and confidence limits will be provided when appropriate. For those subjects for whom an intraoperative blood loss is quantitatively recorded, those data will be collected.

- Minimum level of unbound sum dabigatran concentration at any time since end of the first infusion up to 4 hours after the completion of second infusion will be summarized descriptively. The percentage change of unbound sum dabigatran from pre-dose value to the lowest post-dose value will also be summarized.

- Median and other quantiles of reversal of aPTT and TT at any time point since end of the first infusion up to 4 hours after the completion of the second infusion will be summarized.

For secondary safety endpoints, refer to safety analyses in Section 7.3.4.

[redacted]

### 7.3.4 Safety analyses

The safety analyses will be descriptive in nature and will be based on BI standards. Parameters to be evaluated for safety are described in Section 5.2. Details will be included in the TSAP.

AEs will be coded using the MedDRA dictionary and tabulated by system organ class and preferred term. All AEs will be classified according to the following trial periods: screening, treatment, safety follow-up. All AEs with an onset date/time after the 1st vial of trial medication up to 5 days after the last intake of study medication will be assigned to the treatment period for evaluation. 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. All AEs (including bleeding) in the treatment period will be tabulated in total and according to seriousness, severity and possible relationship to trial medication. AEs in the screening or follow-up period will be listed.

Laboratory data will be analysed both quantitatively and qualitatively.

For assessment of liver function, frequency of patients with elevated ALT/AST or bilirubin will be tabulated. The frequency of potential Hy's Law patients will be provided.

Other lab data, vital signs and physical examinations data will be reported descriptively.

[redacted]

## 7.4 INTERIM ANALYSES

No interim analysis is planned。

## 7.5 HANDLING OF MISSING DATA

With respect to efficacy and safety evaluations, it is not planned to impute missing values. The reversal of anticoagulation cannot be defined if either the pre-dose or all post-dose coagulation test is missing.

### 7.5.1 Plasma concentration – time profiles

Handling of missing PK data will generally be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472, current version).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values). Drug concentration data identified with BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values) with the exception of unbound sum dabigatran. For this analyte, data identified with BLQ following the administration of idarucizumab may be replaced with the lower limit of quantification, until measurable concentrations re-occur. The appropriate time frame will be decided by the TCPK and described in the CTR.

Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, NOA are included).

### 7.5.2 Pharmacokinetic parameters

For the noncompartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. BLQ values for unbound sum dabigatran data will be handled exceptionally; BLQ values will be replaced by the lower limit of quantification which is defined as 1 ng/mL.

The individual pharmacokinetic parameters can be calculated and listed separately. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation

or the complete analysis. If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation. If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However the excluded concentration itself will be listed in the clinical trial report associated with an appropriate flag.

Descriptive statistics of parameters are calculated only when at least 2/3 of the individual parameter estimates of a certain parameter are available. If the actual sampling time will not be recorded or will be missing for a certain time point, the planned time will generally be used for this time point instead. Pharmacokinetic parameters which cannot be determined will be identified by "not calculated" (NC).

### 7.5.3 Pharmacodynamic parameters

With respect to pharmacodynamic evaluations it is not planned to impute missing values. However, clotting times may exceed the maximum clotting time of 500s recorded by the coagulometer, indicating the presence of high concentrations of dabigatran, for example in pre-dose idarucizumab samples. If the blood clotting time exceeds 500s, above the lower limit of quantification (ALQ) will be reported. For calculation of reversal of the anticoagulation effect, ALQ values may be replaced by 500s. BLQ values as well as pharmacodynamic data identified with NOS, NOR and NOA will not be considered.

## 7.6 RANDOMISATION

This trial has a single treatment group without randomisation.

## 7.7 DETERMINATION OF SAMPLE SIZE

The sample size is based only on practical considerations of the frequency of bleeding on dabigatran, the recruitment rates and the number of clinical trial sites that will be initiated. The recruitment of patients who meet the inclusion/exclusion criteria is expected to be slow with an average rate of less than 1 patient per site per year. With an expected 30 sites participating in this study, we anticipate to enroll a total of 20 patients over a period of 1.5 to 2 years or until sufficient patients are enrolled to satisfy the regulatory requirements or until idarucizumab is commercially available in that country.

# 8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 < add if EU countries participate and the protocol falls under the EU regulation 536/2014 > the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) < add if Japan participates > and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

## 8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## 8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

### 8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve

previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

### 8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

### 8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

## 8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

## 8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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 trial

need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

## 8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed insent.

**The end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out"). The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

**Temporary halt of the trial** is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

**Suspension of the trial** is defined as an interruption of the trial based on a Health Authority request.

## 8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the (Investigator Site File) ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Local Clinical Monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

# 9. REFERENCES

## 9.1 PUBLISHED REFERENCES

P09-11669 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et.al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361 (12): 1139 – 1151

P13-01830 Khadzhynov D, Wagner F, Formella S, Wiegert E, Moschetti V, Slowinski T, et.al. A Effective elimination of dabigatran by haemodialysis: a phase I single-centre study in patients with end-stage renal disease. Thromb Haemost 2013; 109: 596 – 605

P13-04186 Liesenfeld KH, Staab A, Haertter S, Formella S, Clemens A, Lehr T. Pharmacometric characterization of dabigatran hemodialysis. Clin Pharmacokinet 2013; 52 (6): 453 – 462

P13-12677 Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, et.al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation 2013; 128 (21): 2325 - 2332 ()

P15-06362 Pollack CV, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, Dubiel R, Huisman MV, Hylek EM, Kamphuisen PW, Kreuzer J, Levy JH, Sellke FW, Stangier J, Steiner T, Wang B, Kam CW, Weitz JI. Idarucizumab for dabigatran reversal. New England Journal of Medicine, online first, published on June 22, 2015, DOI: 10.1056/NEJMoa1502000 N Engl J Med 2015. 373(6):511-520.

## 9.2 UNPUBLISHED REFERENCES

U09-3249-02 [redacted] Randomized Evaluation of Long term anticoagulant therapY (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® STUDY). 16 October 2009. Date of revision: 05 January 2011.

U11-2616-01 Periodic Safety Update Report Pradaxa Dabigatran etexilate hard capsules, 75 mg, 110 mg 19 Sep 2010 to 18 Sep 2011.

U12-3431-02 Investigator's Brochure. 1321.P1. Version 3. 19 Dec 2013.

| | |
|---|---|
| U13-1773-01 | [redacted] Randomised, double-blind, placebo-controlled Phase I study in healthy male volunteers to investigate safety, tolerability and pharmacokinetics of single rising doses of BI 655075 (part 1) and to explore the dose of BI 655075 effective to reverse dabigatran anticoagulant activity (part 2), in preparation. |
| U13-1986-01 | [redacted]In vitro binding affinity of BI 655075 for dabigatran and the functional neutralization of the anticoagulant activity of dabigatran and its acylglucuronides by BI 655075 in vitro in a modified thrombin time assay. Draft version. 30 Oct 2013. |
| 001-MCS-36-472 | Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics |

# 10. APPENDICES

## 10.1 ADVERSE EVENTS DURING TREATMENT IN STUDY 1321.1, PARTS 1 AND 2, IN ORDER OF FREQUENCY

Placebo groups are pooled. Doses of 1000, 2000, and 4000mg with and without dabigatran pre-treatment are pooled. The 5 minute and 1 hour infusions are pooled.

| Dose in mg | 0 (Placebo) | DE alone | 20 | 60 | 200 | 600 | 1000 | 1200 | 2000 | 3000 | 4000 | 6000 | 8000 | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number treated | 36 | 35 | 6 | 6 | 6 | 5 | 15 | 6 | 27 | 6 | 20 | 6 | 6 | 145 |
| Number of AEs during treatment* | 19<br>53% | 32<br>91% | 3<br>50% | 2<br>33% | 9<br>150% | 2<br>40% | 11<br>122% | 1<br>17% | 13<br>62% | 5<br>83% | 8<br>57% | 1<br>17% | 4<br>67% | |
| **Adverse Event** | | | | | | | | | | | | | | |
| Injection site reactions# | 3 | 3 | | | 2 | | 1 | | 6 | 2 | 1 | 1 | 1 | 20 |
| Headache | 4 | 3 | 1 | | 3 | | 1 | | 2 | 1 | 2 | | | 17 |
| Nasopharyngitis | 2 | | | 1 | | 1 | | | 2 | | | | 1 | 7 |
| Dizziness | 1 | 2 | 1 | | | | 1 | | 1 | | 1 | | | 7 |
| Back pain | 1 | 1 | | | | 1 | 2 | | | 1 | 1 | | | 7 |
| Presyncope | | 5 | | | | | | | | | | | | 5 |
| Constipation | | | | | | | 2 | | 1 | | | | | 3 |
| Diarrhea | | 1 | 1 | | | | | | | 1 | | | | 3 |
| Pain in extremity | 1 | | | 1 | | | | | 1 | | | | | 3 |
| Hematuria | | 3 | | | | | | | | | | | | 3 |
| Migraine | | | | | | | | 1 | | | | | 1 | 2 |
| Syncope | 1 | 1 | | | | | | | | | | | | 2 |

| Dose in mg | 0 (Placebo) | DE alone | 20 | 60 | 200 | 600 | 1000 | 1200 | 2000 | 3000 | 4000 | 6000 | 8000 | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number treated | 36 | 35 | 6 | 6 | 6 | 5 | 15 | 6 | 27 | 6 | 20 | 6 | 6 | 145 |
| Number of AEs during treatment* | 19<br>53% | 32<br>91% | 3<br>50% | 2<br>33% | 9<br>150% | 2<br>40% | 11<br>122% | 1<br>17% | 13<br>62% | 5<br>83% | 8<br>57% | 1<br>17% | 4<br>67% | |
| **Adverse Event** | | | | | | | | | | | | | | |
| Epistaxis | 1 | 1 | | | | | | | | | | | | 2 |
| Abdominal pain | | 1 | | | | | | | | | 1 | | | 2 |
| Dyspepsia | | 1 | | | | | 1 | | | | | | | 2 |
| Muscle spasms | 1 | 1 | | | | | | | | | | | | 2 |
| Musculoskeletal stiffness | | | | | 1 | | | | | | | | 1 | 2 |
| Asthenia | | 1 | | | | | | | | | 1 | | | 2 |
| Chest pain | 1 | | | | 1 | | | | | | | | | 2 |
| Bronchitis | | | | | | | | | | | 1 | | | 1 |
| Tonsillitis | | | | | | | 1 | | | | | | | 1 |
| Dizziness postural | | 1 | | | | | | | | | | | | 1 |
| Disgeusia | | 1 | | | | | | | | | | | | 1 |
| Cough | | | | | 1 | | | | | | | | | 1 |
| Palpitations | | 1 | | | | | | | | | | | | 1 |
| Oropharyngeal pain | 1 | | | | | | | | | | | | | 1 |
| Abdominal discomfort | | 1 | | | | | | | | | | | | 1 |

| Dose in mg | 0 (Placebo) | DE alone | 20 | 60 | 200 | 600 | 1000 | 1200 | 2000 | 3000 | 4000 | 6000 | 8000 | Totals |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Number treated | 36 | 35 | 6 | 6 | 6 | 5 | 15 | 6 | 27 | 6 | 20 | 6 | 6 | 145 |
| Number of AEs during treatment* | 19<br>53% | 32<br>91% | 3<br>50% | 2<br>33% | 9<br>150% | 2<br>40% | 11<br>122% | 1<br>17% | 13<br>62% | 5<br>83% | 8<br>57% | 1<br>17% | 4<br>67% | |
| **Adverse Event** | | | | | | | | | | | | | | |
| Abdominal pain upper | 1 | | | | | | | | | | | | | 1 |
| Dysphagia | | 1 | | | | | | | | | | | | 1 |
| Flatulence | 1 | | | | | | | | | | | | | 1 |
| Nausea | | | | | | | 1 | | | | | | | 1 |
| Myalgia | | | | | 1 | | | | | | | | | 1 |
| Chest discomfort | | 1 | | | | | | | | | | | | 1 |
| Fatigue | | 1 | | | | | | | | | | | | 1 |
| Feeling hot | | | | | | | 1 | | | | | | | 1 |
| Influenza like illness | | | | | | | | | 1 | | | | | 1 |
| Glycosuria | | | | | | | | | 1 | | | | | 1 |
| Polyuria | | 1 | | | | | | | | | | | | 1 |

Except for injection site reactions, all AEs are preferred terms
* expressed as number of subjects with events; subjects may report more than one event
#includes infusion site swelling (2 subjects), Injection site hematoma (2), infusion site erythema (2), erythema (2), skin reaction (1), skin irritation (9), catheter site pain (4), and application site irritation (2)

## 10.2 BLOOD DRAW SCHEDULE@

| | | Time | EDTA | Na Citrate | Local aPTT | Safety Lab | Max. Blood Vol (mL) |
|---|---|---|---|---|---|---|---|
| *Visit 1* | *1** | *Baseline* | 12 mL | 4.5 mL | 3 mL | 7 mL | 26.5 |
| Visit 2.1 | | Vial #1 (no blood draw) | | | | | |
| *Visit 2.2* | *2** | *just prior to vial #2* | 6 mL | 4.5 mL | 3 mL | 7 mL | 20.5 |
| | | Vial #2 (no blood draw) | | | | | |
| | *3** | *between 10-30min* | 6 mL | 4.5 mL | 3 mL | 7 mL | 20.5 |
| | 4 | 1 hour +/- 15 min | 6 mL | 4.5 mL | | | 10.5 |
| | 5 | 2hour +/- 30 min | 6 mL | 4.5 mL | | | 10.5 |
| | 6 | 4hour +/- 30 min | 6 mL | 4.5 mL | | | 10.5 |
| | 7 | 12hour +/- 1 hour | 6 mL | 4.5 mL | 3 mL | 7 mL | 20.5 |
| Visit 3 | 8 | 24hour +/- ~~1~~ 2 hour | 6mL | 4.5 mL | | 7 mL | 17.5 |
| Visit 4 | | Day 7 +/- 3 days | | | | | 0 |
| Visit 5 | 9 | Day 30 +/- 7 days | 3 mL | | | | 3 |
| | | APPROXIMATE TOTAL BLOOD VOLUME (MLS) | 57 | 36 | 12 | 35 | 140 |

*Critical samples for assessment of efficacy
EDTA= PK assays, anti-ADA (anti-idarucizumab antibodies)
Na Citrate= Biomarkers,.

@ If a patient requires an additional 5 g dose of idarucizumab, approximately 137mL (baseline to 24 hours) of additional blood may be drawn

## 10.3 CLINICAL LABORATORY EVALUATIONS

| **Central Lab Evaluations** | **Local Lab Evaluations** |
|---|---|
| **PK**<br>1. BI 655075<br>2. anti-BI 655075 antibodies<br>3. Dabigatran (sum and unbound sum)<br>**PD**<br>1. TT | **Standard Safety Lab Panel**<br><br>**Chemistry Panel (includes liver function)**<br>ALT (SGPT)<br>AST (SGOT) |

| | |
|---|---|
| 2. aPTT<br>3. dTT<br>4. ECT | CK (creatine kinase)<br>CK-MB or Troponin if CK is elevated<br>Albumin<br>Alkaline Phosphatase<br>Bilirubin, Total<br>BUN<br>Calcium<br>Cholesterol, Total<br>Chloride<br>Glucose<br>Potassium<br>Protein, Total<br>Sodium<br>Triglycerides<br>Creatinine<br><br>**Hematology Panel**<br>Red Cell Count<br>Red Cell Indices (MCV, MCH, MCHC)<br>White Cell Count<br>White Cell Differential<br>Hemoglobin<br>Hematocrit<br>Platelet Count<br>aPTT<br>**Pregnancy Test** (urine or other rapid test) |

## 10.4 GLASGOW COMA SCALE AND MODIFIED RANKIN SCALE

Glasgow Coma Scale

Eye Opening Response

• Spontaneous--open with blinking at baseline 4 points

• To verbal stimuli, command, speech 3 points

• To pain only (not applied to face) 2 points

• No response 1 point

Verbal Response

• Oriented 5 points

• Confused conversation, but able to answer questions 4 points

• Inappropriate words 3 points

• Incomprehensible speech 2 points

• No response 1 point

Motor Response

• Obeys commands for movement 6 points

• Purposeful movement to painful stimulus 5 points

• Withdraws in response to pain 4 points

• Flexion in response to pain (decorticate posturing) 3 points

• Extension response in response to pain (decerebrate posturing) 2 points

• No response 1 point

References

Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974; 81-84.

Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. Acta Neurochir 1976; 34:45-55.

Categorization: Coma: No eye opening, no ability to follow commands, no word verbalizations (3-8)

Head Injury Classification: Severe Head Injury----GCS score of 8 or less Moderate Head Injury----GCS score of 9 to 12 Mild Head Injury----GCS score of 13 to 15 (Adapted from: Advanced Trauma Life Support: Course for Physicians, American College of Surgeons, 1993).

Disclaimer: Based on motor responsiveness, verbal performance, and eye opening to appropriate stimuli, the Glascow Coma Scale was designed and should be used to assess the depth and duration coma and impaired consciousness. This scale helps to gauge the impact of a wide variety of conditions such as acute brain damage due to traumatic and/or vascular injuries or infections, metabolic disorders (e.g., hepatic or renal failure, hypoglycemia, diabetic ketosis), etc. Glasgow Coma Scale (continued from previous page) May 9, 2003 Page 2 of 2

Education is necessary to the proper application of this scale. Teasdale G, Kril-Jones R, van der Sande J. Observer variability in assessing impaired consciousness and coma. J Neurol Neurosurg Psychiatry 1978; 41:603-610; Rowley G, Fielding K. Reliability and accuracy of the Glasgow Coma Scale with experienced and inexperienced users. Lancet 1991; 337:535-538). The predictive value of the GCS, even when applied early, is limited (Waxman K, Sundine MJ, Young RF. Is early prediction of outcome in severe head injury possible? Arch Surg 1991; 126:1237-1242).

Despite these and other limitations (Eisenberg HM. Outcome after head injury: Part I: general Considerations, in Becker DP, Povlishock JR (eds): Central Nervous System Trauma Status Report, 1985. Washington, DC: U.S. Government Printing Office, 1988:271-280), health care practitioners continue to use this practical scale widely.

Source: Adapted from Glasgow Coma Scale, Womack Army Medical Center, Fort Bragg, NC.

Modified Rankin Scale

| Score | Description |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out all previous activities, but able to look after own affairswithout assistance |
| 3 | Moderate disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |

| | |
|---|---|
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention |
| 6 | Dead |

References

Rankin J. “Cerebral vascular accidents in patients over the age of 60.”
*Scott Med J* 1957;2:200-15

Bonita R, Beaglehole R. “Modification of Rankin Scale: Recovery of motor function after stroke.”
*Stroke* 1988 Dec;19(12):1497-1500

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. “Interobserver agreement for the assessment ofhandicap in stroke patients.”

*Stroke* 1988;19(5):604−7

## 10.5 PHARMACOKINETIC METHODS

$C_{pre,}$ $C_{min,1,}$ $C_{max}$ and $t_{max}$: Individual $C_{max}$ and $t_{max}$ values will be directly determined from the plasma concentration time profiles of each patient. If the same $C_{max}$ concentration occurs at different time points, $t_{max}$ is assigned to the first occurrence of $C_{max}$.

gMean, gCV: The geometric mean (gMean) and coefficient of variation, gCV (given in %), will be calculated by the formulae:

$$\text{gMean} = \exp\left[\frac{1}{n}\sum_{i=1}^{n}\ln(x_i)\right] = \exp\left[\overline{\ln(x_i)}\right]$$

$$\text{gCV}(\%) = 100 \cdot \sqrt{\exp\left[\text{Var}(\ln(x_i))\right] - 1}$$

where

$$\mathrm{Var}(\ln(x_i)) = \frac{1}{n-1}\sum_{i=1}^{n}\left[\ln(x_i) - \overline{\ln(x_i)}\right]^2$$

## 10.6 CLINICAL EVALUATION OF LIVER INJURY

### 10.6.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.6.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

### 10.6.2 Procedures

Repeat the following lab tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours. If ALT and/or AST >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF;

and report these via the CRF.

*Clinical chemistry*
alkaline phosphatase, albumin, PT or INR, CK, CK-MB or Troponin , coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

*Serology*
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG. If anti-IgM and anti-IgG are not available, total anti Hep D can be performed), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody <project dependent:> Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)>

Hormones, tumormarker
**TSH**

*Haematology*
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

- Initiate close observation of patients by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

# 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol

## 11.1 GLOBAL AMENDMENT 1

| | | |
|---|---|---|
| **Date of amendment** | | |
| **EudraCT number**<br><br>**EU number** | | |
| **BI Trial number** | | |
| **BI Investigational Product(s)** | | |
| **Title of protocol** | | |

| | |
|---|---|
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | |
| **To be implemented immediately in order to eliminate hazard –**<br><br>**IRB / IEC / Competent Authority to be notified of change with request for approval** | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | |
| | |

| | | |
|---|---|---|
| **Section to be changed** | | |
| **Description of change** | | |
| **Rationale for change** | | |

## 11.2 GLOBAL AMENDMENT 2

| | | |
|---|---|---|
| **Date of amendment** | | |
| **EudraCT number**<br><br>**EU number** | | |
| **BI Trial number** | | |
| **BI Investigational Product(s)** | | |
| **Title of protocol** | | |

| | |
|---|---|
| **To be implemented only after approval of the IRB / IEC / Competent Authorities** | |
| **To be implemented immediately in order to eliminate hazard –**<br><br>**IRB / IEC / Competent Authority to be notified of change with request for approval** | |
| **Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only** | |
| | |

| | | |
|---|---|---|
| **Section to be changed** | | |
| **Description of change** | | |
| **Rationale for change** | | |

**APPROVAL / SIGNATURE PAGE**

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**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Approval–Clinical Monitor | [redacted] | 02 Jun 2017 03:23 CEST |
| Author-Trial Statistician | | 02 Jun 2017 04:46 CEST |
| Approval-Team Member Medicine | | 02 Jun 2017 18:04 CEST |
| Author-Trial Clinical Pharmacokineticist | | 05 Jun 2017 03:56 CEST |
| Approval-Therapeutic Area [redacted] | | 05 Jun 2017 20:17 CEST |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|