Clinical Trial Protocol

	Document Number:	**c08884404-01**
EudraCT No.: **EU Trial No:**	2015-002177-37	
BI Trial No.:	1321.7	
BI Investigational Product(s):	Idarucizumab	
Title:	Single dose, open label, uncontrolled, safety trial of intravenous administration of idarucizumab to paediatric patients enrolled from ongoing phase IIb/III clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism.	
Lay Title:	Reversal of dabigatran anticoagulant effect with idarucizumab.	
Clinical Phase:	III	
Trial Clinical Monitor:	Phone: / Fax:	
Coordinating Investigator:	Phone: / Fax:	
Status:	Final Protocol	
Version and Date:	**Version: 1.0**	**Date: 4 February 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim			
Name of finished product: Praxbind			
Name of active ingredient: Idarucizumab			
Protocol date: 4 February 2016	**Trial number:** 1321.7		**Revision date:**

Title of trial:	Single dose, open label, uncontrolled, safety trial of intravenous administration of idarucizumab to paediatric patients enrolled from ongoing phase IIb/III clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism.
Coordinating Investigator:	Phone: / Fax:
Trial sites:	Multi-centre trial, approximately 25 to 40 sites
Clinical phase:	III
Objectives:	To demonstrate the safety of idarucizumab, as assessed by the occurrence of patients with drug related adverse events (including immune reactions) and all-cause mortality in paediatric venous thromboembolism (VTE) patients treated with dabigatran in ongoing clinical trials who require emergency surgery/urgent procedures or patients who have life-threatening or uncontrolled bleeding which requires urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is needed.
Methodology:	Open label, uncontrolled, case series
No. of patients:	Approximately 5 patients
total entered:	Approximately 5 patients
each treatment:	Not applicable (there is only one treatment, idarucizumab)
Diagnosis :	Patients from trials 1160.106 and 1160.108 in selected sites in 10 countries treated with dabigatran etexilate who require rapid reversal of the anticoagulant effect of dabigatran prior to emergency surgery/urgent procedures or patients who exhibiting signs and symptoms of life-threatening or uncontrolled bleeding requiring urgent medical intervention are eligible.

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Main criteria for inclusion:	Group A: Patients who are taking dabigatran etexilate and have life-threatening or uncontrolled bleeding requiring urgent medical or surgical intervention. Group B: Patients who are taking dabigatran etexilate who are not bleeding, but do require emergency surgery/urgent procedures for a condition other than bleeding, where therapeutic anticoagulation with dabigatran is undesirable.
Test product(s):	Idarucizumab in buffered solution for injection 50 mL/vial, 50 mg/mL
dose:	The total dose is up to 5g based on patient's weight, given as rapid infusions/injections, divided in two equal parts administered no more than 15 minutes apart.
mode of administration:	Intravenous
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment	Two equal parts of idarucizumab administered no more than 15 minutes apart.
Endpoints	Primary endpoint: The primary endpoint is the safety of idarucizumab in a paediatric population as assessed by the occurrence of drug-related adverse events (including immune reactions) and all-cause mortality during the trial. Secondary endpoints: • Percent change of coagulation tests (dTT, ECT) at 30 minutes post-dose compared to pre-dose. • Time to achieve complete reversal of dabigatran effect, based on coagulation tests (dTT and ECT).

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	• Duration of complete reversal of dabigatran effect sustained at 24 hours post-dose, based on coagulation tests (dTT and ECT). • Cessation of bleeding (Group A patients only).* • Bleeding status and other clinical conditions that may contribute to bleeding (Group A patients only) during the trial.* • Development of treatment-emergent antidrug antibodies (ADA) with cross reactivity to idarucizumab at 30 days post-dose of idarucizumab.* *This is a safety issue.
Safety criteria:	Adverse events, local tolerability, immune reactions, thrombo-embolic events, mortality, vital signs (blood pressure (BP), heart rate (HR)), laboratory tests (including hepatic and renal function, haematology, clinical chemistry, coagulation parameters, antidrug antibodies against idarucizumab).
Statistical methods:	Descriptive statistics for efficacy, safety and PK/PD endpoints will be reported, if deemed appropriate. For most endpoints, data will be listed due to limited number of patients. Sufficient numbers of treated patients to do subgroup analysis are not expected. The two patient groups (life-threatening or uncontrolled bleeding patients and those requiring emergency surgery/urgent procedures) will be summarized separately and together, with an overall conclusion, if possible.

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 Trial)**
Visit Description	Patient screening[1] (baseline)	Dosing (vial 1)	Dosing (vial 2)	24-hours after dosing	7 days after dosing	30 days after dosing
Visit Day(s)	1	1	1	2	7	30
Time window for visit			no later than 15 minutes after vial 1	± 2 hours	± 3 days	+ 7 days
Informed consent / assent[2]	X					
Inclusion / exclusion criteria	X					
Confirm current dabigatran etexilate use	X					
Medical History	X					
Demographics	X					
Physical Exam	X					
Height	X					
Weight	X					
Body Temperature	X					
Vital Signs (blood pressure and heart rate)	X	X[3]	X[3]	X[3]	X[3]	X
Bleeding assessment[4]	X	X	X	X	X	X
Surgery/Procedure assessment[5]	X	X	X	X	X	X
Trial Drug Administration[6]		X	X			
PK/PD Blood Draw[7]		X	X	X		
Blood draw for idarucizumab antidrug antibodies[7]		X				X
Local Safety Blood Draw[8]	X			X		
Optional local aPTT/other local tests[8]		(X)	(X)	(X)		
Pregnancy Testing[9]	X					X
Trial drug accountability			X			
ECG	X				X	
Adverse Events	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X
Re-start anticoagulant therapy[10] (if applicable)				(X)		
Conclusion of patient participation[11]						X

[1] Due to the need for urgent care in these patients, it is anticipated that the majority of screening procedures will have already been performed as part of the hospitalisation and diagnosis procedures. These procedures should not be repeated for the purpose of the trial. Any trial procedures that were not performed as part of routine care must only be performed after informed consent has been obtained.

Collection of medical history and other standard of care information up to the time of consenting must be provided as source documents as part of the study screening procedures and will be collected on the eCRF.

[2] The informed consent (and if applicable assent) should be obtained per local legislations and guidelines from the patient and/or the patient's legally accepted representative where applicable before any trial procedures are performed.

[3] Blood pressure and heart rate will be measured approximately hourly while the patient is in the emergency or similar department, then approximately every 6 to 8 hours for the next 72 hours or until discharge, whichever comes first.

[4] Bleeding severity for the index bleed (Group A) or any unusual bleed associated with surgery (Group B). Bleeding assessments during Treatment Period should be done at or near times of blood draws. The definitions for bleeding are based on recommendations made by the Perinatal and Paediatric Haemostasis Subcommittee during the 56th-58th Scientific and Standardization Committee (SSC) Meetings of the ISTH (R11-4225), refer to section 5.3.5.

[5] Group B patients only (refer to section 3.3.1). Surgery/procedure assessments during Treatment Period should be done at or near times of blood draws.

[6] Actual times for the start and end of the dosing of idarucizumab is to be recorded.

[7] Refer to appendix 10.2 for detailed blood draw schedules. The pre-dose lab assessment is the baseline lab assessment.

Pre-dose and between vials sampling: central blood sampling for pharmacodynamic biomarkers (dTT, ECT, aPTT, TT), pharmacokinetics (dabigatran and idarucizumab concentration) will occur immediately prior to administration of each vial of idarucizumab. Blood sampling for idarucizumab ADA will only occur prior to vial 1 administration.

Post-dose sampling: central blood sampling for pharmacodynamic biomarkers (dTT, ECT, aPTT, TT), pharmacokinetics (dabigatran and idarucizumab concentrations) will be collected at 30 minutes (± 10 minutes), 4 hours (± 30 minutes), 12 hours (± 1 hour) and 24 hours (± 2 hours) post-dose. Blood sampling for idarucizumab ADA will occur 30 days (+7 days) post-dose.

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children. E.g. omission of exploratory coagulation markers, reduced frequency of safety labs during the treatment period, etc.

Refer to appendix 10.3 for detailed information (priority order of lab parameters).The decision for reduced blood collection in those cases will be documented in the medical notes and CRF.

Time will be recorded for every blood sample taken.

[8] Includes Haematology and Chemistry. Optional local blood draws for aPTT and other local lab testing may be done at the discretion of the treating physician to facilitate patient clinical management.

[9] Local urine or other appropriate spot pregnancy test in female adolescents of child bearing potential (patients who have reached menarche). More frequent testing can be done if required by the local regulation and/or authority or per Investigator's judgement. Enrolment of pregnant patients is not allowed.

[10] Re-start of anticoagulant therapy, if applicable, can be a return to dabigatran etexilate for patients from Group B. Patients from Group A have to be switched to a standard of care anticoagulant medication.

[11] Also needs to be completed if the patient withdraws prematurely following first vial of trial medication or at any later time point prior end of trial.

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ABBREVIATIONS

ADA	Anti Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AF	Atrial Fibrillation
ALQ	Above upper Limit of Quantification
ALT	Alanine-Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate-Aminotransaminase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BID	bis in die (twice daily dosing)
BLQ	Below lower Limit of Quantification
BP	Blood Pressure
CA	Competent Authority
CHO	Chinese Hamster Ovary (cells)
CI	Confidence Interval
CML	Local Clinical Monitor
Cpre	Concentration of the analyte in plasma prior to first trial medication dose
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CVL	Central Venous Line
DEDP	Drug Exposure During Pregnancy
DMC	Data Monitoring Committee
dTT	diluted Thrombin Time
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
EDC	Electronic Data Capture
EDTA	Ethylenediamine Tetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
EOT	End of Treatment
ER	Emergency Room
EudraCT	European Clinical Trials Database
Fab	Monoclonal Antibody Fragment
FAS	Full Analysis Set
FEIBA	Factor Eight Inhibitor Bypassing Activity
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HFI	Hereditary Fructose Intolerance
HPC	Human Pharmacology Centre
HR	Heart Rate
IB	Investigator's Brochure
IC50	Half Maximal Inhibitory concentration

IEC	Independent Ethics Committee
IMP	Investigational Medicine Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISTH	International Society for Thrombosis and Haemostasis
i.v.	intravenous
K	Potassium (chemical element)
LPDD	Last Patient Drug Discontinuation
MBE	Major Bleedings
MedDRA	Medical Dictionary for Drug Regulatory Activities
Na	Sodium (chemical element)
NOA	Not Analysed
NOR	No Valid Result
NOS	No Sample Available
NVAF	Non-Valvular Atrial Fibrillation
PD	Pharmacodynamics
PE	Pulmonary Embolism
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PCC	Prothrombin Complex Concentrate
RBC	Red Blood Cells
RDC	Remote Data Capture
REP	Residual Effect Period, after the last dose of medication with measurable drug levels or pharmacodynamic effects still likely to be present
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SSC	Scientific and Standardization Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBMA	Trial Biomarker Analyst
TBV	Total Blood Volume
TCM	Trial Clinical Monitor
TCPK	Trial Clinical Pharmacokineticist
TDMAP	Trial Data Management and Analysis Plan
TSTAT	Trial Statistician
TT	Thrombin Time
TBV	Total Blood Volume
ULN	Upper Limit of Normal
VTE	Venous Thromboembolism (Venous Thrombotic Event)

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Anticoagulation therapy is a mainstay of treatment and prevention of pathologic thrombosis in different clinical settings. Several direct 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 and uncontrolled bleeding, remains a relevant side effect. With the increasing use of direct oral anticoagulants such as dabigatran etexilate, there is an unmet medical need for reversal agents that could be used in rare or uncommon emergency situations to reverse the anticoagulant effects of these drugs.

Dabigatran is a direct thrombin inhibitor, a potent anticoagulant that is the active principle of the prodrug, dabigatran etexilate (Pradaxa®). This drug has been approved for short term treatment in the prevention of thromboembolism following orthopaedic surgery and for chronic treatment for stroke prevention in patients with non-valvular atrial fibrillation (NVAF). Furthermore, dabigatran etexilate is approved for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Dabigatran treatment in non-valvular atrial fibrillation patients in the RE-LY trial showed superior efficacy over warfarin with the 150 mg bis in die (BID) dose with similar bleeding rate and non-inferiority with the 110 mg BID dose, with an improved bleeding profile (P09-11669)

As with all anticoagulants, bleeding was the most common side effect in the RE-LY trial, with major bleeding occurring at a rate of approximately 3% /year and life-threatening bleeding at a rate of 1.5% /year in patients with NVAF.

The RELY extension trial, RELY-ABLE (P13-08115) provided additional safety information for a large cohort of patients which continued the same dose of dabigatran etexilate as assigned in the RE-LY trial. During additional 2.5 years of treatment with maximum exposure of over six years in both trials, the long-term safety of dabigatran etexilate was confirmed. The rate of bleedings was consistent with those seen in RE-LY.

In a pooled analysis of acute venous thromboembolism (VTE) treatment studies, the rate of major bleedings (MBE) was lower in patients taking dabigatran etexilate compared to warfarin patients (2.1 vs 3.6 MBE/100 patient-years) (P13-16985)

Post-marketing surveillance has also shown that major and fatal bleeding events have been reported in some patients taking dabigatran since its approval (U11-2616-01). In the subset of patients where demographic data is available, the majority (57%) had renal clearance <30 mL/min and were elderly (over 75 years). While the observed cases are not in excess of the rates of bleeding seen in the RE-LY trial, an effective method of reversing the anticoagulant effect of dabigatran in patients would be desirable under exceptional circumstances. In addition to this, the need for immediate reversal of anticoagulation in patients on dabigatran etexilate who require emergency surgery, for example a patient with acute appendicitis, is another intended use of the reversal agent.

Similar to in adults, the use of a reversal agent could complement the management of life-threatening bleeding events or urgent surgery in the paediatric population, but in a vanishingly small number of patients.

Dabigatran etexilate is not yet licensed for use in paediatric patients. The target indication for dabigatran etexilate in paediatric patients is VTE treatment/secondary prevention. The incidence of symptomatic thrombosis is approximately 5.1 per 100,000 live births, 2.4 per 1000 neonatal intensive care admissions and 1 case per 100,000 paediatric patients (R06-2301; R07-2937; P94-81556). Recent studies have shown that the incidence of VTE in children is increasing, creating a new epidemic in paediatric tertiary care (R13-4252; R13-4256). The annual rate of VTE in USA was increased over time to 58 cases per 10,000 hospital admissions (R09-5148), paediatrics 2009). About 50% of paediatric thromboses occur in children aged 12-18 years. Teenage girls have twice the rate of VTE compared to teenage boys, due to the use of oral contraceptives and due to pregnancy. Over 50% of VTEs in children occur in the upper venous system secondary to the use of central venous lines (CVL).

Dabigatran etexilate exposure worldwide is in excess of 5 million patient-years in adults. However, only bleeding events arising from clinical trials in paediatric patients, off label use or unintentional use/suicide attempts could account for any bleeding events observed in children to date.

For the assessment of off-label use data from all reporting sources have been considered, nearly all evaluated patients were adults. Taking global exposure of dabigatran etexilate into account, off-label use ranged, between 2.9% and 3.6% of all assessable cases, depending upon definition (cases reporting only off-label indications resp. all cases reporting any off-label indication together with labelled indications) (s00034702-01).

Worldwide 37 case reports on the use of dabigatran etexilate in children have been received by Boehringer Ingelheim (BI) since launch of Pradaxa® in March 2008 (s00034702-01). The reporting sources were spontaneous (25), Health Authorities (5), literature (5) and clinical trials (2). In 9 (24.3%) of the 37 cases a bleeding event has been reported. These events, except of those received from clinical trials, have occurred in off-label use of dabigatran etexilate. There were 5 case reports of dabigatran etexilate overdose (1.65g – 6g dabigatran etexilate) in children; in none of these children the intake of dabigatran etexilate was associated with bleeding. Based on the data provided, there is currently little off label use of dabigatran in children.

Clinical trials of dabigatran etexilate in paediatric patients are described in the EMA-approved Paediatric Investigation Plan (PIP) for dabigatran etexilate. The PIP requires the investigation of the condition “Venous Thromboembolic Events treatment (secondary venous thrombotic event prevention)”. The PIP also includes a waiver for the indications “primary venous thrombotic event prevention” and “thromboembolic event prevention in atrial fibrillation” (EMEA-000081-PIP01-07-M07). Therefore, the potential future commercial use of idarucizumab will be limited to the paediatric population receiving dabigatran etexilate for the treatment /secondary prevention of VTEs.

To date, clinical trials of dabigatran etexilate in paediatric patients in the indication of treatment of VTE have been limited to early stage pharmacokinetics and formulation studies. There have not been any reports of bleeding or risk of bleeding associated with the need for urgent intervention in these trials. Clinical investigations with dabigatran etexilate in the paediatric population are targeted to be concluded in coming years.

Idarucizumab (Praxbind®) is a specific reversal agent for dabigatran and is currently approved in several countries worldwide (including USA and European Union) in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required (P16-00177).

Three randomised, double-blind, placebo-controlled Phase I studies in 283 subjects (224 treated with idarucizumab) were conducted to assess the safety, efficacy, tolerability, pharmacokinetics and pharmacodynamics of idarucizumab, given alone or after administration of dabigatran etexilate. The investigated population consisted of healthy subjects and subjects exhibiting specific population characteristics covering age, body weight, race, sex and renal impairment. In these studies the doses of idarucizumab ranged from 20 mg to 8 g and the infusion times ranged from 5 minutes to 1 hour.

Representative values for pharmacokinetic and pharmacodynamics parameters were established on the basis of healthy subjects aged 45-64 years receiving 5 g idarucizumab.

A prospective, open-label, non-randomized, uncontrolled trial (RE-VERSE AD) is currently ongoing (at time of finalising this protocol) to investigate the treatment of adult patients who presented with dabigatran-related life-threatening or uncontrolled bleeding (Group A) or who required emergency surgery or urgent procedures (Group B). The primary endpoint was the maximum percentage reversal of the anticoagulant effect of dabigatran within 4 hours after the administration of idarucizumab, based on central laboratory determination of dilute thrombin time (dTT) or ecarin clotting time (ECT). A key secondary endpoint is the restoration of haemostasis.

An interim analysis of RE-VERSE AD included data for the first 90 adult patients: 51 patients with serious bleeding (Group A) and 39 patients requiring an urgent procedure (Group B) (P15-06362; P15-12457).

Complete reversal (100%) of the anticoagulant effect of dabigatran as measured by dilute thrombin time (dTT) or ecarin clotting time (ECT) after administration of idarucizumab was achieved in all but one patient. Unbound sum dabigatran serum concentrations fell below 20 mg/mL (a level that produces little or no anticoagulant effect) immediately after administration of idarucizumab, resulting in normalisation of dTT and ECT. Normal intraoperative haemostasis was reported in 92% of patients who underwent an urgent procedure. At 12 and 24 hours after idarucizumab administration, 93% and 79% of patients respectively had unbound sum dabigatran serum concentrations < 20 ng/mL; whether patients with rising dabigatran concentrations would benefit from another dose of idarucizumab is not known.

The safety and efficacy of idarucizumab in children is not yet established and will be investigated in this trial.

Clinical trials of idarucizumab in paediatric patients are described in the EMEA-approved Paediatric Investigation Plan for idarucizumab (EMEA-001438-PIP01-13).

The target population of this trial will be patients who are being treated with dabigatran etexilate within the currently running paediatric clinical trials for treatment (trial 1160.106) or secondary prevention (trial 1160.108) of VTE.

Trial 1160.106 is an active-controlled, open-label, randomized, parallel-group, trial designed to confirm a proposed dabigatran etexilate dosing algorithm and to assess the safety and effectiveness of dabigatran etexilate compared to standard of care for treatment of VTE in children from birth to less than 18 years of age.

Trial 1160.108 is an open label, single arm prospective cohort trial designed to assess the safety of dabigatran etexilate for secondary prevention of VTE in children from birth to less than 18 years of age.

Based on the adult RE-LY trial results (P09-11669) and the planned recruitment in the above two paediatric studies, it is expected to have two or three bleeds requiring urgent intervention in these two trials. However, given that the primary risk factors for bleeding are age > 75 years and high drug exposure (due to low creatinine clearance), the bleed rates in children may be much lower than those seen in RE-LY. Regardless of which probabilities apply, these numbers are clearly insufficient by themselves to reach reliable conclusions regarding safety and efficacy of idarucizumab in children.

Nevertheless, the availability of idarucizumab as reversal agent in these trials could further improve the benefit/risk assessment of dabigatran etexilate use even if treatment of only a few patients with idarucizumab is possible.

1.2 DRUG PROFILE

Drug Substance and Drug Product

Idarucizumab (BI 655075) 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 Chinese hamster ovary (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).

It is expected that most patients will only be treated once. Exposure to the reversal agent a second time, for a new event that may be weeks or even years after the first event, is expected to be infrequent or rare.

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 a half maximal inhibitory concentration (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.

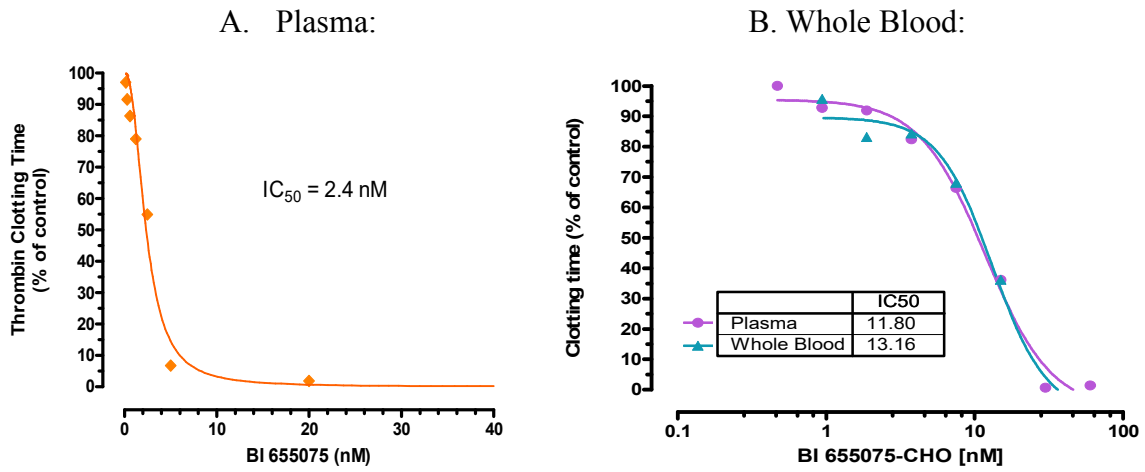

Figure 1.2: 1 The reversal of anticoagulant activity of dabigatran by idarucizumab in human plasma (A) and whole blood (B). (U13-1986-01)

Reversal of anticoagulation was then tested in a rat model in vivo. Dabigatran was given as initial bolus and then 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). 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 (dark purple line). This reversal by a single bolus was maintained for the 30 minute dabigatran infusion. Measurement of aPTT also resulted in a similar pattern.

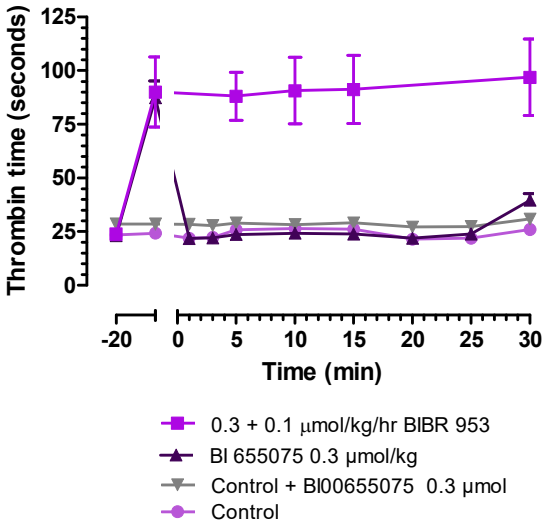

Figure 1.2: 2 The neutralization of dabigatran activity measured as thrombin time after addition of BI 655075 at t = 0. Data expressed as mean ± SE, n = 4-6 (U13-1986-01)

Further pharmacology studies have been performed in a rat tail cut bleeding model. Dabigatran etexilate was administered orally at a dose of 30 mg/kg. Forty five minutes after oral administration of dabigatran etexilate, idarucizumab (33 mg/kg or 0.69 µmol/kg) was administered as a single bolus and bleeding was also reversed within 5 min. This effect was also maintained for up to 2 hours after the single bolus dose. Further sampling for up to 6 hours did not result in any re-emergence measurable dabigatran anticoagulation in the circulation.

The reversal of the anticoagulant effect of dabigatran was also tested in these experiments. Using the diluted thrombin time, it could be demonstrated that the functional dabigatran levels achieved were approximately 1200 nM or ~ 600 ng/mL prior to idarucizumab administration. This is far in excess of therapeutic levels of dabigatran achieved in subjects receiving the 150 mg BID dose (peak/trough 184/90 ng/mL) (P10-03790). Anticoagulation was completely reversed within 5 min of idarucizumab administration. However, a small amount of functional dabigatran anticoagulant activity was measurable 30 min after administration (~120 nM, or 60 ng/mL) and remained at this low level for the duration of the experiment. This level of dabigatran anticoagulation did not result in bleeding.

Thus, these studies demonstrate a potent, rapid and specific reversal of the anticoagulant and bleeding effects of dabigatran both in human plasma in vitro and in the rat.

For a more detailed description of the idarucizumab drug profile, please refer to the current Investigator's Brochure (IB) (U12-3431).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Idarucizumab has been examined in adult patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects was required (P15-06362). The safety and efficacy of idarucizumab in children is not yet established and will be investigated in this trial.

The present trial will be performed in the context of the PIP of idarucizumab as agreed with the European Medicines Agency. The proposed indication of idarucizumab are patients treated with dabigatran etexilate who require emergency surgery/urgent procedures where rapid reversal of the anticoagulant effects of dabigatran is needed or patients who have life-threatening or uncontrolled bleeding which requires urgent intervention.

Some anticoagulants have a specific reversal agent that can be used when rapid reversal is required, e.g. protamine sulphate is used for the heparins. Current recommendations for management of bleeding with the new agents are symptomatic and non-specific. They include supportive measures such as replacing fluid volumes, administering fresh frozen plasma and/or packed red blood cells and identifying the site of bleeding (P10-03790).

There are two possible scenarios where paediatric use of idarucizumab might occur, bleeding associated with VTE treatment/secondary VTE prevention (potential future dabigatran etexilate paediatric indication), or requirement for emergency surgery or urgent intervention while receiving dabigatran etexilate. Without such data, the comparison of the aetiology or outcomes of these conditions in children with the same conditions in the adult population becomes extremely difficult. One cannot compare prevalence, incidence, treatment methods, or alternative treatments. Therefore evaluations of the similarities/differences of the condition between adult and paediatric populations are currently theoretical. It is however reasonable to assume that dabigatran associated bleeding or risk of excessive bleeding in case of emergency surgery can occur in a paediatric population.

This trial is designed to demonstrate the safety of idarucizumab in paediatric patients. The reversal of anticoagulant activity will be demonstrated by analysing the biomarker data in a central laboratory, independent of the clinical management of the patient. Changes in these biomarkers will not be used to make clinical decisions about patient care. Patient outcomes will, however, be collected and reported.

2.2 TRIAL OBJECTIVES

The trial objective is to demonstrate the safety of idarucizumab, as assessed by the occurrence of patients with drug related adverse events (including immune reactions) and all-cause mortality in paediatric VTE patients treated with dabigatran in ongoing clinical trials who require emergency surgery/urgent procedures or patients who have life-threatening or uncontrolled bleeding which requires urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is needed.

2.3 BENEFIT - RISK ASSESSMENT

Administration of idarucizumab to a dabigatran etexilate treated patient will reverse the anticoagulant effect of dabigatran.

Idarucizumab (Praxbind®) is a specific reversal agent for dabigatran and is currently approved in several countries (including USA and the European Union) in adult patients treated with dabigatran etexilate (Pradaxa®) when rapid reversal of its anticoagulant effects is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding.

The safety of idarucizumab has been evaluated in 224 healthy subjects as well as in an ongoing phase III trial 123 adult patients, who required emergency surgery/urgent procedures or had life-threatening or uncontrolled bleeding and were under treatment with dabigatran etexilate. No drug related adverse reactions have been identified in this interim evaluation.

The safety and efficacy of idarucizumab in children below the age of 18 years have not yet been established. Paediatric dosing of idarucizumab is considered proportional to the patient's body weight (refer to section 4.1.2)

The potential risk of immune reactions, if occurring, will be managed under expert care in the emergency room (ER) or similar department.

Compared to adult renal function, the human infant has decreased renal blood flow during the first months of life, but increased glomerular filtration rate (GFR) thereafter (R04-1541). GFR in humans increases after birth and reaches adult levels at 1-2 years of age. Immature glomeruli are present for the first months after birth and glomerular maturation and filtration increase during early infancy. GFR in children above 1-2 years of age is in general higher compared to adults.

Literature review has revealed no information regarding differences in protein size filtration of glomeruli in children versus adults. Therefore, it is assumed that idarucizumab will be filtered by the kidneys of children in a manner similar to adults, albeit more slowly in neonates, but somewhat quicker in infants due to the differences in GFR.

The idarucizumab formulation contains 220 mM sorbitol as an excipient, i.e., 40 mg/mL, which may be of concern in individuals with Hereditary Fructose Intolerance (HFI). HFI is a relatively rare genetic disorder estimated to occur in 1 in 20,000 individuals that results in intolerance of fructose-containing food. HFI generally becomes apparent during weaning, when foods containing fructose are introduced into the diet and signs of intolerance become evident, e.g., vomiting, nausea, abdominal pain, and sweating, associated with hypoglycaemia and metabolic acidosis (R13-1338). As sorbitol is metabolized to fructose, precautions related to HFI are relevant to foods and pharmaceutical formulations containing sorbitol. It is suggested that sorbitol (fructose) exposure in paediatric patients with HFI be limited to 40 mg/kg (R13-1336; R13-1337), which is equivalent to 1 mL/kg of the

idarucizumab formulation, to avoid biochemical changes. Therefore, children with known HFI will be excluded from the trial.

Juvenile toxicity

Idarucizumab will be excreted by the kidneys. It may bind to the megalin/cubulin receptors in the proximal tubules and undergo re-uptake and catabolism in the proximal tubule cell lysozymes, and the amino acids re-used by the body. Alternately, it is excreted into the urine and perhaps a small amount is catabolized by the liver. It is recognized that dabigatran bound to idarucizumab is likely also to be taken up through megalin/cubulin into renal proximal tubule cells, with potential for toxicity. However, there is no evidence of renal proximal tubule cell toxicity in the animal studies conducted. In a pivotal 2-week monkey study, monkeys received dabigatran etexilate orally, followed 1.5 hour later by intravenous idarucizumab. Therefore, monkeys were exposed for 14 consecutive days to the dabigatran: idarucizumab complex, with no evidence of toxicity observed in the kidneys (i.e., no clinical pathology or microscopic changes). Toxicity studies showed no target organ toxicity following administration of idarucizumab.

Juvenile animal studies are only conducted when organ systems affected or potentially affected by the compound are immature or notably different between adults and the targeted paediatric population. As nephrogenesis is complete at birth in humans and renal capacity in children is equivalent to or better than that of adults, there is no reason to perform juvenile animal studies to support trials in children. Therefore, no juvenile animal studies have been performed or are planned with idarucizumab.

Blood sampling

Blood sampling for all parameters listed for this trial (safety laboratory, pharmacokinetics and biomarkers) together with blood sampling in trial 1160.106 or 1160.108) should not exceed the maximum blood volume limits recommended by the European Commission (R10-4959) nor the maximum specified in local guidelines (if applicable). Refer to section 5.3.3 and appendix 10.3.

Given the expected benefits from reversal of dabigatran effects in paediatric patients requiring emergency surgery/urgent procedures or those patients with life-threatening or uncontrolled bleeding, the available adult safety data and the safety precautions in this trial, the current benefit/risk assessment is considered to be favourable.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1. OVERALL TRIAL DESIGN AND PLAN

The trial will be an open-label, multicentre, multinational trial, with a single treatment arm, consisting of idarucizumab. The target population will be patients who are being treated with dabigatran etexilate within the currently running paediatric clinical trials for treatment (trial 1160.106) or secondary prevention (trial 1160.108) of VTE.

The patients may either require emergency surgery/urgent procedures where therapeutic anticoagulation would, in the opinion of the treating clinician, unduly increase the risk of intra- and post-operative bleeding, or patients may have life-threatening or uncontrolled bleeding which requires urgent intervention.

There are two separate but related elements in this trial, 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 removed 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 (such as a PTT).

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 the reversal agent 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 (if feasible).

Reversal of anticoagulant activity will be recorded in all patients treated with idarucizumab (unless blood sampling is limited by blood volume, bleeding and/or distress considerations especially in very young children based on Investigator's judgement).

The patients may be identified in ambulances or at the emergency or similar department of participating hospitals. After determination that the patient has been treated with dabigatran etexilate in an ongoing trial, the informed consent/assent process will occur and visit procedures as described in section 6 will be followed.

Due to the need for urgent care in these patients, it is anticipated that the majority of screening procedures as noted in the Flow Chart will already have been performed as part of the hospitalisation and diagnosis procedures. These procedures should not be repeated for the purpose of the trial. Any trial procedures that were not yet performed as part of routine care must only be performed after informed consent (and assent if applicable) has been obtained.

Collection of medical history and other standard of care information up to the time of consenting must be provided as source documents as part of the study screening procedures and will be collected on the eCRF.

During the emergency situation, until the last visit in this trial (Visit 5), the patients will participate in the dabigatran trial 1160.106 or 1160.108 and in this trial, at the same time with the unscheduled visit procedures of the 1160.106 or 1160.108 being applied together with the screening procedures for this trial.

After Visit 5 in this trial, patients remain in the 1160.106 or in the 1160.108 trial according to the applicable protocol.

Procedures, results and adverse events occurring during the time of participation in this trial will be recorded in both trials, i.e. 1321.7 and 1160.106 or 1160.108, respectively.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim. Patients will be enrolled from dabigatran trial 1160.106 or trial 1160.108 in approximately 25 to 40 sites in about 10 countries.

A Coordinating Investigator is responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities are defined in a contract.

The same data-monitoring committee (DMC) as established for dabigatran paediatric trials 1160.106 and 1160.108, independent of the sponsor will be used to assess the progress of the clinical trial, including a safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings. Since this is an open-label trial, all information sent to the DMC is unblinded.

Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the Investigator Site File (ISF).

Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), 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 internal 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.

The safety laboratory investigations will be performed at the Investigator's site as well as the ECGs.

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

3.2. DISCUSSION OF TRIAL DESIGN

The current trial is designed to evaluate safety in paediatric patients who received dabigatran within the currently running paediatric clinical trials with dabigatran (1160.106 and 1160.108) and require emergency surgery/urgent procedures or have life-threatening or uncontrolled bleeding, as well as to track the clinical course and outcomes of the patients during their acute episode requiring reversal of anticoagulation.

Each patient will have an assessment of immune reactions, adverse events and mortality. Safety assessment is the primary goal. Clinical endpoints such as patient status, whether the bleeding stops or diminishes may vary widely depending on the clinical situation, will be evaluated. Local measurements of coagulation and central pharmacodynamics (PD) (biomarkers) and pharmacokinetic (PK) measurements will also be evaluated. By providing baseline and post-treatment clotting time assessments, each patient acts as his own control.

This trial will evaluate use of idarucizumab in a paediatric population during the development of dabigatran etexilate (1160.106 and 1160.108 clinical trials) in the target paediatric indication (VTE treatment/ secondary prevention) where idarucizumab could be provided as reversal agent for dabigatran.

Recruitment of patients will be challenging. The frequency and timing of emergency surgery or bleeding in this paediatric population cannot be predicted in advance. Is also difficult to predict, where the patient will be treated for the bleeding. Furthermore, for a variety of clinical reasons, some patients may be treated with intensive support and symptomatic treatments such as red blood cell transfusion instead of actual reversal of anticoagulation.

As a result the number of suitable patients for recruitment in this trial will be low. To not limit the patient potential for this trial, there is no staggered (age-dependent) recruitment approach. However, due to the age related staggered approach in trials 1160.106/1160.108, it is expected that first patients in trial 1321.7 will be in age range of 12 to 18 years.

3.3. SELECTION OF TRIAL POPULATION

Eligible paediatric patients from trial 1160.106 or 1160.108 treated with dabigatran etexilate who require emergency surgery/urgent procedures requiring rapid reversal of the anticoagulant effect of dabigatran prior to these emergency surgery/urgent procedures or

patients who exhibiting signs and symptoms of life-threatening or uncontrolled bleeding requiring urgent medical intervention, could participate.

Recruitment of patients is expected to be slow with an average rate of less than 1-2 patients per year. The target number of total entered (treated and evaluable) patients in this trial is five.

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

Should the same patient present twice during his/her participation in trial 1160.106 or in trial 1160.108 with the need for a reversal of the anticoagulant effect of dabigatran according to the selection criteria below, this will be allowed, irrespective of the time elapsed between previous participation in the trial and the new participation.

In line with protocols 1160.106 or 1160.108, this is only possible for dabigatran etexilate treated patients from group B (refer to section 3.3.1) requiring an emergency procedure or surgery who can be re-started dabigatran etexilate treatment after their treatment with idarucizumab, patients from Group A (refer to section 3.3.1), with a major bleeding, have to switch to standard of care after the bleeding episode.

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 life-threatening or uncontrolled bleeding requiring urgent medical or surgical intervention.

Group B:
Patients who are taking dabigatran etexilate who are not bleeding, but do require emergency surgery/urgent procedures for a condition other than bleeding, where therapeutic anticoagulation with dabigatran 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

Patients taking dabigatran etexilate in the paediatric trials 1160.106 or 1160.108 are eligible for this trial if they meet the following criteria:

Group A:

1. Overt bleeding judged by the treating physician to require a reversal agent.

2. Currently taking dabigatran etexilate in the context of a clinical trial with dabigatran etexilate (1160.106 or 1160.108).

3. Male or female patients from 0 to less than 18 years of age at the time of informed consent/assent for participation in trial 1160.106 or in trial 1160.108.

4. Female patients of childbearing potential (defined as having experienced menarche) must have followed the contraception requirements according to the dabigatran trial 1160.106 or trial 1160.108 in which they are enrolled.

5. Written informed consent provided by the patient (and/or the patient's legally accepted representative) and assent provided by the patient (if applicable) at the time of informed consent signature in accordance with GCP and local legislation prior to admission to the trial. If the child is unable to give assent at the time of the emergency, the assent, when applicable will be obtained as soon as feasible.

Group B:

1. A condition requiring an emergency surgery or invasive procedure where adequate haemostasis is required. Emergency is defined as need for surgery or intervention within the following 8 hours.

2. Currently taking dabigatran etexilate in the context of a clinical trial with dabigatran etexilate (1160.106 or 1160.108).

3. Male or female patients from 0 to less than 18 years of age at the time of informed consent/assent for participation in trial 1160.106 or in trial 1160.108.

4. Female patients of childbearing potential (defined as having experienced menarche) must have followed the contraception requirements according to the dabigatran trial 1160.106 or trial 1160.108 in which they are enrolled.

5. Written informed consent provided by the patient (and/or the patient's legally accepted representative) and assent provided by the patient (if applicable) at the time of informed consent signature in accordance with GCP and local legislation prior to admission to the trial. If the child is unable to give assent at the time of the emergency, the assent, when applicable will be obtained as soon as feasible.

3.3.3 Exclusion criteria

Group A:

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

2. Patients with no clinical signs of bleeding.

3. Patients with body weight < 2.5 kg

4. Contraindications to trial medication including known hypersensitivity to the drug or its excipients; e.g. patients with known hereditary fructose intolerance who may react to sorbitol.

5. Female patients who are pregnant, nursing, or who plan to become pregnant while in the trial.

Group B:

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

2. Patients with body weight < 2.5 kg

3. Contraindications to trial medication including known hypersensitivity to the drug or its excipients; e.g. patients with known hereditary fructose intolerance who may react to sorbitol.

4. Female patients who are pregnant, nursing, or who plan to become pregnant while in the trial.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

Screening failures
Patients who do not meet one or more of the entry criteria or discontinue prior to trial medication treatment will be considered as screening failures. They have to be recorded as screening failure in eCRFs and no further follow-up is required.

Withdrawal trial treatment

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

- The patient and/or the patient's legally accepted representative withdraws consent for trial treatment or trial participation, without the need to justify the decision,
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication,
- 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.

If the patient and/or the patient's legally accepted representative withdraws informed consent for trial treatment or trial participation prior trial treatment, the trial will end for that patient. Patient has to be recorded as screening failure in eCRF and no further follow-up is required.

Once a patient receives trial medication, all observations outlined in the protocol should be performed.

Withdrawal of trial participation:

If a patient and/or the patient's legally accepted representative withdraws trial participation after receiving trial treatment, the last trial visit (Visit 5) 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.

For all patients the reason for withdrawal must be recorded in the eCRF. These data will be included in the trial database and reported.

Trial treatment is defined as patients who have received at least one vial of trial medication. Completion of the trial is defined as patients who complete all trial visits.

3.3.4.2 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. Advice of the independent DMC, decision by an Independent Ethics Committee (IEC) /Institutional Review Board /(IRB) or Competent Authority (CA)
2. Failure to meet expected enrolment goals overall or at a particular trial site
3. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
4. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract disturbing 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 intravenously as two consecutive infusions over 5 to 10 minutes each or as two bolus injections. There is no comparator treatment.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product idarucizumab

Substance:	Idarucizumab (BI 655075)
Pharmaceutical formulation:	Solution for injection/infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co KG Germany
Unit strength:	2.5 g per 50 mL vial
Posology	Up to 5.0 g (dose divided in two equal parts)
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 colourless 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

Paediatric dosing of idarucizumab is considered proportional to the patient's body weight from 300 mg to 5000 mg, where 5000 mg is a reference dose of the patient with body weight of 71 kg and above. This is based on the assumption that also the total body load of dabigatran at a given plasma concentration range scales approximately with weight. A target plasma concentration range for dabigatran is targeted with a nomogram-based dosing in the current paediatric dabigatran program (refer to protocol 1160.106/.108).

Based on the assumption that dabigatran plasma levels achieved in children are in the same range as for adults, the approach was taken to down-scale idarucizumab paediatric dosing based on body weight.

This dosing approach assumes that distribution of dabigatran in children is not significantly different from adults, and that the dabigatran load per kg of body weight is similar.

Therefore, dose calculation based on body weight extrapolates the overwhelming idarucizumab dose concept from adults to children (P15-06362).

The overwhelming dose concept makes potential minor differences in dabigatran load per kg irrelevant for efficacy.

Also taking the WHO growth standards for paediatric population into consideration, the body weight category below 10 kg was split into two groups. Actually, this group represents the paediatric population below one year, and it is split into new-borns and infants below 6 kg and older infants from 6 to 10 kg (refer to the Table 4.1.2: 1). Infants with body weight below 2.5 kg are not included in Boehringer Ingelheim's VTE paediatric program; therefore, this group will not be included in the idarucizumab paediatric program.

For determination of the weight category of a patient, the patient's weight will be rounded up or down to the kilogram with a cut off at 0.5 kg. For example, a patient's weight from 5.000 kg up to 5.499 kg will be rounded down to 5 kg while a patient's weight from 5.500 kg up to 5.999 kg will be rounded up to 6 kg for calculation of the dose to be administered.

It is expected that the mechanism of action of idarucizumab will be identical in paediatric and adult populations since it involves the binding affinity of two external molecules, dabigatran and idarucizumab. The affinity of idarucizumab for dabigatran is extremely high and specific. Whether the binding of the two molecules takes place in the circulation of children or adults should not make any difference. Based on the preclinical information, the mechanism of action, and the expected clearance of idarucizumab, the renal function of the patient may however play a critical role in the clearance of the idarucizumab-dabigatran complex. Differences in the amount of dabigatran, the amount of idarucizumab, or clearance of either agent might affect the time course of the effect.

The target human dose for adults was estimated based on equimolar neutralization of the total body load of dabigatran. This approach has previously been used to successfully calculate the dose of an anti-digoxin Fab to treat digoxin overdose (R11-1174). Total body burden of dabigatran was calculated using two distinct approaches:

- Based on observed peak dabigatran concentration multiplied by the known volume of distribution and
- Based on the dose and taking into account a dabigatran bioavailability of about 6.5% as well as an accumulation of about 1.7 fold.

Both approaches result in similar amounts for dabigatran total body burden. An idarucizumab dose of 1.4 or 2 grams was therefore calculated to neutralize dabigatran anticoagulation based on mean dabigatran exposure after 150 or 220 mg dabigatran etexilate BID, respectively, in adults. For details of the calculations refer to the Investigator's brochure (U12-3431).
An overwhelming dose of 5 g is being used in adults, as determined by modelling, to

neutralize anticoagulant activity of dabigatran in patients with higher dabigatran exposure (90 percentile).

Table 4.1.2: 1 Idarucizumab paediatric dosing according to body weight

Weight (kg)		**Idarucizumab paediatric dosing according to body weight***		
from	**to**	**Rounded idarucizumab total dose, mg**	**Rounded idarucizumab total dose, ml**	**Application schedule of idarucizumab (split dose applications)**
2.5	5	300	6	2 x 3 ml
6	10	600	12	2 x 6 ml
11	20	1250	25	2 x 12.5 ml
21	30	1850	37	2 x 18.5 ml
31	40	2500	50	2 x 25 ml
41	50	3100	62	2 x 31 ml
51	60	3750	75	2 x 37.5 ml
61	70	4350	87	2 x 43.5 ml
71	80	5000	100	2 x 50 ml
81	90	5000	100	2 x 50 ml
91	100**	5000	100	2 x 50 ml

* Based on adult dose for 80 kg patient of 5000 mg Idarucizumab
**A patient with body weight > 100 kg will be dosed with 5000 mg idarucizumab as well.

4.1.3 Method of assigning patients to treatment groups

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

4.1.4 Drug assignment and administration of doses for each patient

Drug dispensing may occur via the hospital pharmacy or a secure storage location in the emergency or similar department of the trial centre. Each 50 mL vial contains 2500 mg of idarucizumab. For both Group A and Group B, the first part of the dose (from vial 1) 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 the second part of the dose (from vial 2), no later than 15 minutes after the end of the first part of the dose.
The infusion/injection is recommended to be filtered using an in-line 0.2 µm filter.

The detailed preparation procedures for the injections and the material to be used for the preparation can be found in the "Guidelines for IMP Management, Dispensing and Administration" which is stored in the ISF.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Not applicable. There is only one treatment in this open-label trial.

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.

Trial medication may only be administered to trial patients according to the protocol and prepared in strict observance of the preparation procedures and conditions as described in the ISF.

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 trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the head of 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,
- For USA, availability of Form 1572.

The Investigator or Pharmacist 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 or appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

All used (empty or partially filled) vials should be saved for verification by the CRA in accordance with local practice. Once verified, the vials will be destroyed on site according to the facility policy for destruction of biologic material. Used vials should be kept in the kit box if possible. Any patient information placed on the vial must be de-identified (e.g. any pharmacy labelling that contains patient name or date of birth) or removed.

All unused trial medication will be returned to BI (or designated contractor) at the end of the trial or at the time of stock replacement when IMP is past the expiration date. Details of the return procedure are provided in the ISF. Throughout the duration of the trial, drug receipt, usage and return must be documented and verified. Any discrepancies in drug supplies will be noted and explained.

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, or packed platelets are permitted. Administration of activated prothrombin complex concentrates (e.g. FEIBA) or recombinant Factor VIIa, or concentrates of coagulation factors II, VII, IX, or X may be considered, even though their use has not been evaluated in clinical trials. Dabigatran can be haemodialysed out of the patient's circulation. Approximately 60% of the drug can be removed over 2-3 hours: however, there is limited clinical data supporting this approach (P13-01830, P13-04186).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

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 idarucizumab may remain circulating for up to 24 hours after infusion (less than 1% of the dose in patients with normal renal function, but somewhat more in patients with renal insufficiency or failure). This may impact the expected efficacy of reinstituted anticoagulation with dabigatran.

In patients who stopped taking dabigatran etexilate due to an emergency surgery or other invasive procedure (Group B patients, refer to section 3.3.1), dabigatran etexilate treatment can be re-initiated 24 hours after administration of idarucizumab, if the patient is clinically stable and adequate haemostasis has been achieved. Re-initiation of dabigatran etexilate is not allowed in Group A patients.

If there is an urgent indication to re-start anticoagulation after trial 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 at any time prior to re-initiation of dabigatran. In patients with creatinine clearance <30 mL/min dabigatran 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

Female patients who are not of reproductive potential (i.e. pre-pubertal) are not considered to have childbearing potential and therefore do not need to use contraception to be eligible for the trial.

Female patients who have reached menarche are considered to have childbearing potential and must use acceptable method(s) of birth control as indicated in trial 1160.106 or 1160.108 wherein the patients are enrolled.

4.3 TREATMENT COMPLIANCE

The trial drug is administered as an intravenous injection/infusion in the emergency or similar department of the trial centre. The administrations start and stop times of the first and second injection/infusion for administration of the total dose will be recorded. Any interruptions or discontinuations of infusions will also be recorded. Refer to Section 4.1.4 for method of administration.

5 VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is the safety of idarucizumab in a paediatric population as assessed by the occurrence of drug-related adverse events (including immune reactions) and all-cause mortality during the trial.

5.1.2 Secondary Endpoints

The reversal of anticoagulant activity and formation of antidrug antibodies (ADA) will be recorded in all patients (unless limited by blood volume, bleeding and/or distress considerations, especially in very young children).

Reversal of the anticoagulant effect of dabigatran at time *t* is defined as: [a]

$$\text{Reversal}\ (t) = \frac{\text{predose coagulation test} - \text{postdose coagulation test at time } t}{\text{predose coagulation test} - \text{ULN}} \times 100\%$$

Values equal to or higher than 100% will be interpreted as complete reversal of the anticoagulant effect. The reversal of anticoagulant activity will be based on central lab measurements.

The following are the secondary endpoints:

- Percent change of coagulation tests (dTT, ECT) at 30 minutes post-dose compared to pre-dose.
- Time to achieve complete reversal of dabigatran effect[a], based on coagulation tests (dTT and ECT).
- Duration of complete reversal of dabigatran effect[a] sustained at 24 hours post-dose, based on coagulation tests (dTT and ECT).
- Cessation of bleeding (Group A patients only).[b]
- Bleeding status and other clinical conditions that may contribute to bleeding (Group A patients only) during the trial.[b]
- Development of treatment-emergent ADA with cross reactivity to idarucizumab at 30 days post-dose of idarucizumab.[b]

[a] The ULN for each marker has been determined using data from idarucizumab phase I trials 1321.1 (U13-1773-01) and 1321.2 (c02742738). It was calculated as the (arithmetic) mean + 2*SD using all data collected prior to the dosing of dabigatran

and the data from patients who were on placebo as well as pre-dose data from idarucizumab alone treatment (as available). SD denotes the standard deviation.

[b] This is a safety issue.

5.2 ASSESSMENT OF EFFICACY

The efficacy of idarucizumab will be assessed based on the central laboratory measurement of anticoagulant activity by dTT and ECT (secondary endpoints), aPTT and TT (further endpoints) tests. Further endpoints include the measurement of the unbound sum (free) plasma concentrations of dabigatran.

5.3 ASSESSMENT OF SAFETY

Adverse events, local tolerability, immune reactions, thrombotic events, mortality, vital signs blood pressure, heart rate, laboratory tests (including hepatic and renal function, haematology, clinical chemistry and idarucizumab ADA) will all be part of the safety assessment.

5.3.1 Physical examination

A complete physical examination (including cardiac, neurological, dermatological, pulmonological examinations, etc), height/length (in cm), body weight (in kg) and body temperature in °C will be performed at screening with record of abnormalities on the Medical History/Baseline Conditions eCRF page. Weight measurement should be done on the age-appropriate scale and preferably in the same conditions as used to measure the dabigatran dose in the 1160.106 or 1160.108 trial wherein the patient is enrolled.

New abnormal findings or worsening of baseline conditions detected in later examinations during the trial will be recorded as AEs on the appropriate eCRF page.

5.3.2 Vital Signs

Blood pressure and heart rate will be recorded at time points noted in the Flow Chart.

5.3.3 Safety laboratory parameters

Safety laboratory parameters will be performed by the local laboratories of the trial centres as noted in Flow Chart. Standard safety lab panel may include when feasible, the following measurements:

Haematology:

Red blood cell count, haemoglobin, haematocrit, white blood cell count and differential, platelets

Chemistry:

Glucose, albumin, total protein, sodium, potassium, chloride, urea, creatinine, alanine aminotransaminases (ALT), aspartate aminitransaminases (AST), alkaline phosphatase, total bilirubin or conjugated (direct)/unconjugated (indirect)

Pregnancy test (if applicable):

Local urine or other appropriate spot pregnancy test in female adolescents of child bearing potential (patients who have reached menarche) at time points as noted in the Flow Chart . More frequent testing can be done if required by the local regulation and/or authority or per Investigator's judgement. Enrolment of pregnant patients is not allowed.

Lab abnormalities:

Any local lab abnormalities should be followed-up per Investigator's judgement.

Blood sampling volume:

All efforts should be made to use the lowest amount of blood per sample as technically possible by using special paediatric collection systems. Blood sampling for this trial and for dabigatran trial 1160.106 or 1160.108 should not exceed the maximum blood volume limits recommended by the European Commission nor the maximum specified in local guidelines (if applicable), i.e. blood loss should not exceed 3% of the total blood volume (TBV) over four weeks and should not exceed 1% of the TBV at any single time (R10-4556; R10-4959).

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children.

Cross reporting of lab results might be applied (across studies 1160.106, 1160.108 and this trial) in order not to increase the blood volume required for analysis.

Refer to appendix 10.2 for further details of blood sampling.

Blood draws for pharmacokinetics, biomarkers, ADA can be found in section 5.4, section 5.5 and section 5.6. Refer also to the Flow Chart.

5.3.4 Electrocardiogram

An ECG will be performed at time points as noted in the Flow Chart. Documentation of, and findings from ECGs, must be part of the source documents available at the site.

Printed paper tracings from 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be collected and stored at the site. In the event of any cardiac symptoms or ECG abnormalities

(i.e. heart rhythm disorders, PR prolongation, QRS enlargement, QT prolongation, etc.), additional ECGs will be recorded. All ECGs will be evaluated (signed, dated and commented upon) by the treating physician/Investigator and stored locally. Any clinically relevant changes (according to Investigator's judgement) in the ECG will be reported as AEs and followed up and/or treated locally until a normal or stable condition if feasible is achieved.

All ECGs performed at any time during the conduct of the trial (whether clinically relevant or routine) will be stored in the patient source notes.

5.3.5 Other safety parameters

5.3.5.1 Bleeding assessment

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 recommendations made by the Perinatal and Paediatric Haemostasis Subcommittee during the 56th-58th Scientific and Standardization Committee (SSC) Meetings of the ISTH (R11-4225).

Baseline assessment:

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

Bleeding assessment

Major bleeding:

- Fatal Bleeding.
- Clinically overt bleeding associated with a decrease in haemoglobin of at least 2 g/dL (20 g/L) in a 24 hour period.
- Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system.
- Bleeding that requires surgical intervention in an operating suite.

Clinically relevant non-major bleeding:

- Overt bleeding for which a blood product is administered and which is not directly attributable to the patient's underlying medical condition,
- Bleeding that requires medical or surgical intervention to restore haemostasis, other than in an operating suite.

Minor bleeding:

- Minor bleeds are any overt or macroscopic evidence of bleeding that does not fulfil the criteria for either major bleeding or clinically relevant, non-major bleeding.

- In cases where haemoglobin or haematocrit values are not available for Group A patients during the conduct of the trial then bleeding assessments may be assessed retrospectively based on data associated with the post-dose time points.

5.3.5.2 Assessment of other conditions potentially contributing to bleeding

Any other clinical condition that may contribute to bleeding such as major trauma or the use of antiplatelets, etc. will be assessed as well.

5.3.6 Assessment of adverse events

5.3.6.1 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.

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

Serious adverse event
A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this 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
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"
Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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 given above.

The latest list of "Always Serious AEs" can be found in the RDC 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. AESI need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

No AESIs have been defined for this trial.

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

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

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

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

Arguments that may suggest 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.

5.3.6.2 Adverse event collection and reporting

AE <u>Collection</u>
The Investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate eCRF(s):

- From signing the informed consent until individual patient's end of trial (Visit 5):
  - all AEs (serious and non-serious)

After the individual patient's end of trial the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs of which the Investigator may become aware of on a SAE form.

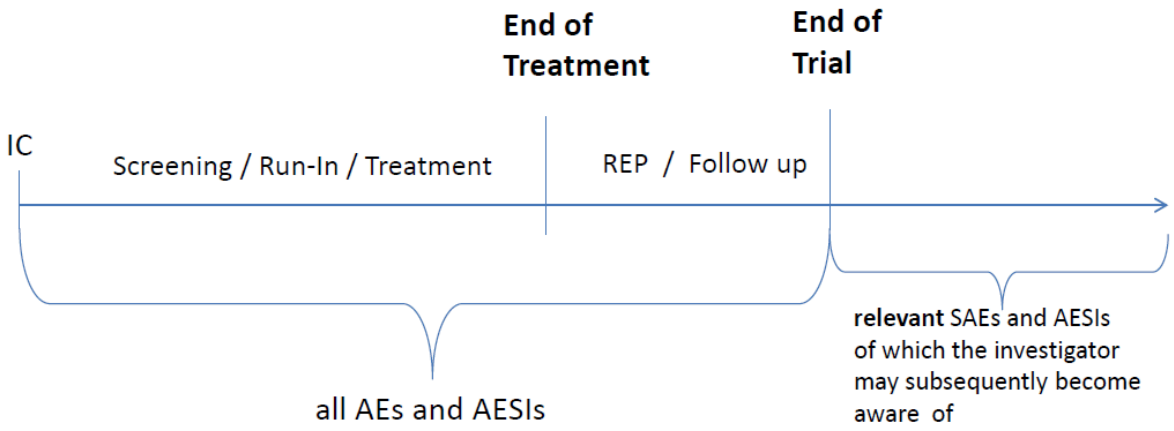

Figure 5.3.6.2: 1 Types of AEs to be reported according to the trial period. No AESIs have been identified for this trial.

The REP is defined as 24 hours after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment, please refer to section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

Events leading to emergency surgery/urgent procedures qualifying for enrolment in this trial will be captured as an SAE or Outcome Event in the current dabigatran trial (trial 1160.106 or 1160.108) as appropriate.

Bleeding events qualifying for enrolment in this trial (index bleeding events) will be captured as SAE in the current dabigatran trial (trial 1160.106 or 1160.108).

AE reporting to sponsor and timelines
The Investigator must report SAEs and non-serious AEs which are relevant for the reported SAE, 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 CRF pages and the BI SAE form.
The following should also be recorded as an (S)AE in the eCRF and 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 trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE associated with the pregnancy an SAE form must be completed in addition.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

Pharmacokinetic endpoints are listed in section 5.1.3 under further endpoints.

Idarucizumab plasma concentrations will be listed. Due to the infrequent blood sampling it is not planned to calculate PK parameters.

If feasible, PK parameters for idarucizumab may be estimated using pharmacometric methods. In that case, the respective results are not planned to be presented in the clinical trial report but in a separate, stand-alone report.

In addition, the following PK parameter will be determined for sum dabigatran, as feasible:
- C_{pre} (concentration of the analyte in plasma prior to first idarucizumab administration)

In addition, the following PK parameter will be determined for unbound sum dabigatran, as feasible:
- C_{pre} (concentration of the analyte in plasma prior to first idarucizumab administration)

5.4.2 Methods of sample collection

The total amount of blood for central lab assessments of pharmacokinetics of idarucizumab, and dabigatran and the anti-drug antibody assay is indicated in appendix 10.2.

Blood collection supplies for central lab measurements will be provided.

K-EDTA blood samples will be collected at time points specified in the Flow Chart and in appendix 10.2 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)

Actual clock times must be recorded for every sample. For the early time points after drug administration, samples should be obtained from a site that is remote from the idarucizumab infusion. If this is not possible an appropriate volume of blood should be voided prior to sampling per treated physician's judgement. Start the blood sampling with K-EDTA collection tubes followed by Na-Citrate tubes (for biomarker sampling, refer to section 5.5.3). Immediately after blood sampling, the drawing tubes should be gently inverted about 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 logistic lab preferably within one day after the 24 hours post-dose blood sampling.
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 / lab manual.

Validated methods will be used for all analytes.

5.4.3 Analytical determinations

A central lab will process and ship samples to the analytical labs involved.

5.4.3.1 Analytical determination of idarucizumab plasma concentrations

Idarucizumab concentrations will be determined using validated enzyme-linked immunosorbent assay (ELISA) methods. Detailed descriptions of the assays will be available prior to the start of sample analysis.

Samples will be analysed at:

The sponsor may appoint other laboratories for method development and sample analysis, if necessary.

5.4.3.2 Analytical determination of dabigatran plasma concentrations

Concentrations of dabigatran will be determined by validated HPLC-MS/MS assays (high performance liquid chromatography, tandem mass spectrometry) at

Plasma samples will be analysed at:

The sponsor may appoint other laboratories for method development and sample analysis, if necessary.

5.5 ASSESSMENT OF BIOMARKERS

5.5.1 Biobanking

This is not applicable in this trial.

5.5.2 Coagulation biomarkers

Coagulation biomarkers are the basis for determination of efficacy in this trial. In some countries or regions some biomarkers maybe only for investigational use (e.g. diluted Thrombin Time).

Biomarker assays will be measured in a central laboratory.
1. Ecarin Clotting Time (ECT)
2. diluted Thrombin Time (dTT)
3. activated Partial Thromboplastin Time (aPTT)
4. Thrombin Time (TT)

The following parameter will be calculated 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)

5.5.3 Methods of sample collection

Blood will be collected into sodium citrate collection tubes (3.2%) to obtain at least 500 µL (microL) citrate plasma at each time point for central laboratory evaluation of dTT, ECT,

aPTT and TT at planned time points as noted in the Flow Chart and indicated in appendix 10.2 and appendix 10.3. For further details on sample handling and shipment please refer to the central lab manual.

5.5.4 Analytical determinations

The blood coagulation parameters activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), diluted thrombin time (dTT, FIIa inhibition by Hemoclot® assay) and thrombin time (TT) will be investigated.

Samples will be analysed at:

The sponsor may appoint other laboratories for method development and sample analysis, if necessary.

5.6 OTHER ASSESSMENTS

5.6.1 Idarucizumab antidrug antibodies assay

An antidrug antibodies assay will be performed for idarucizumab at planned time points as noted in Flow Chart.

5.6.2 Methods of sample collection

K-EDTA blood samples will be collected at time points specified in the Flow Chart and in appendix 10.2 order to prepare plasma.

5.6.3 Analytical determination of idarucizumab antidrug antibodies

Human anti-idarucizumab antibodies will be detected in human plasma samples by a validated bridging ECL method. Samples will be screened for ADA. Putative positive samples will be tested in a confirmation assay, and positive samples will also be titered and characterized for epitope specificity. Detailed descriptions of the assays will be available prior to the start of sample analysis.

Samples will be analysed at:

The sponsor may appoint other laboratories for method development and sample analysis, if necessary.

5.7 APPROPRIATENESS OF MEASUREMENTS

The choice of central lab measurement of coagulation tests dTT, ECT for secondary endpoints is explained in section 3.2. Clinical outcomes such as bleeding reduction, bleeding cessation, duration of hospitalisation, and clinical status of the patient will be recorded.

Coagulation tests such as dTT, ECT, aPTT and TT, are the tests used in the evaluation of a medication with this mechanism of action.

Some tests may be for investigational use only in specific countries, e.g. dTT. 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 coagulation factor concentrates on the reversal with idarucizumab; animal studies of PCCs show some improvement in bleeding.

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

6 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Eligible patients will receive trial medication after meeting inclusion and exclusion criteria. All patients who receive trial 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 trial medication must undergo End of Trial (Visit 5) procedures.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening Period

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

When a patient presents to the investigative team, given consent by the patient (and/or the patient's legally accepted representative) and assent provided by the patient (if applicable and feasible to provide by the patient at the time of the emergency), meets all inclusion/exclusion criteria, the patient will be eligible to participate in the trial.

Due to the need for urgent care in these patients, it is anticipated that the majority of screening procedures will have already been performed as part of the hospitalisation and diagnosis procedures. These procedures should not be repeated for the purpose of the trial. Any trial procedures that were not performed as part of routine care must only be performed after informed consent (and assent if applicable) has been obtained.

Collection of medical history and other standard of care information up to the time of consenting must be provided as source documents as part of the study screening procedures and will be collected on the eCRF.

After obtaining informed consent (and assent if applicable) for the trial the following procedures will be performed unless they have already been performed as part of routine procedures for hospitalisation and diagnosis:

- Bleeding assessments for the index bleed (Group A) or any unusual bleed associated with surgery (Group B, if applicable).
- Surgery/procedure assessment (Group B, if applicable).
- Perform local urine or other appropriate spot pregnancy test in female adolescents of child bearing potential (patients who have reached menarche). Enrolment of pregnant patients is not allowed.

- Draw blood for local lab safety evaluation
- ECG
- Record concomitant therapy
- Record adverse events
- Record demographics, medical history and physical examination (including height, weight and temperature) and vital signs.

6.2.2 Treatment Period

Trial medication will consist of two vials of 2.5g idarucizumab (total dose up to 5.0g, according to body weight, refer to Table 4.1.2: 1) administered no longer than 15 minutes apart. In most cases, written informed consent (and assent if applicable) and treatment with the trial medication will be on the same day.

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children.

Visit 2.1 (Day 1 continued):

Observations and Procedures:

- Draw blood immediately prior to vial 1 administration for central lab parameters (biomarkers, PK and ADA). Record time of blood draw (= baseline lab assessment).
- Administer first dosing from first vial of trial medication. Record start and stop time of administration.
- Bleeding assessments for the index bleed (Group A) or any unusual bleed associated with surgery (Group B, if applicable).
- Surgery/procedure assessments (Group B, if applicable).
- Measure blood pressure and heart rate approximately hourly while the patient is in the emergency department (or similar department), then approximately every 6 to 8 hours for the next 72 hours or until patient is discharged, whichever comes first.
- Record adverse events
- Record concomitant therapies
- Optional (local) aPTT measurement or other local test

Visit 2.2 (Day 1 continued):

Observations and Procedures:

- Draw blood immediately prior to vial 2 administration, for central lab parameters (biomarkers, PK). Record time of blood draw.
- Administer second dosing from second vial of trial medication no later than 15 minutes after the completion of the first vial. Record start and stop time of administration.

- Draw blood 30 minutes (± 10 minutes), 4 hours (± 30 minutes) and 12 hours (± 1 hour) post-dose for central lab parameters (biomarkers and PK). Record time of blood draw.
- Bleeding assessments for the index bleed (Group A) or any unusual bleed associated with surgery (Group B). Bleeding assessments at or near times of blood draws.
- Surgery/procedure assessments at or near times of blood draws (Group B patients).
- Measure blood pressure and heart rate approximately hourly while the patient is in the emergency or similar department, then approximately every 6 to 8 hours for the next 72 hours or until patient is discharged, whichever comes first.
- Record adverse events
- Record concomitant therapies
- Perform trial drug accountability
- Optional (local) aPTT measurement or other local test

6.2.3 Safety Follow-Up Period

Visit 3: 24-hour after dosing (+/- 2 hours)

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children.

Observations and procedures

- Draw blood 24 hours post-dose for central lab parameters (biomarkers and PK). Record time of blood draw.
- Draw blood 24 hours post-dose for local lab safety evaluation. Record time of blood draw.
- Bleeding assessment for the index bleed (Group A) or any unusual bleed associated with surgery (Group B). Bleeding assessment at or near time of blood draw.
- Surgery/procedure assessment at or near time of blood draw (Group B patients).
- Measure blood pressure and heart rate approximately hourly while the patient is in the emergency department (or similar department), then approximately every 6 to 8 hours for the next 72 hours or until patient is discharged, whichever comes first.
- Record adverse events
- Record concomitant therapies
- Re-start appropriate anticoagulant therapy (at treating physician/Investigator discretion)
- Optional (local) aPTT measurement or other local test

Visit 4: 7 days after dosing (+/- 3 days)

Observations and procedures

- Bleeding assessment for the index bleed (Group A) or any unusual bleed associated with surgery (Group B).
- Surgery/procedure assessment (Group B patients only).
- Measure blood pressure and heart rate (approximately hourly if the patient is still in the emergency or similar department, then approximately every 6 to 8 hours for the next 72 hours or until patient is discharged), whichever comes first.
- ECG
- Record adverse events
- Record concomitant therapies

Visit 5: End of Trial 30 days after dosing (+ 7 days)

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children.

Observations and procedures:

- Bleeding assessment for the index bleed (Group A) or any unusual bleed associated with surgery (Group B). Bleeding assessment at or near time of blood draw.
- Surgery/procedure assessment at or near time of blood draw (Group B patients only).
- Measure blood pressure and heart rate
- Draw blood for central lab parameters (ADA). Record time of blood draw.
- Perform local urine or other appropriate spot pregnancy test in female adolescents of child bearing potential (patients who have reached menarche).
- Record adverse events
- Record concomitant therapies
- 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 open-label trial to assess the safety of idarucizumab and to evaluate the reversal of the anticoagulant effects of dabigatran by intravenous administration of idarucizumab to paediatric patients treated with dabigatran etexilate who have life-threatening or uncontrolled bleeding or who have require emergency surgery/urgent procedures. The two patient groups (patients having life-threatening or uncontrolled bleeding and those requiring emergency surgery/urgent procedures) will be summarized separately and together, with an overall conclusion, if possible.

The primary and secondary endpoints will be reported using descriptive statistics or using listings due to limited number of patients in each group. Descriptive statistics will be performed, when appropriate from a sample size perspective. Statistical inference will not be performed. Sufficient numbers of treated patients to do subgroup analysis are not expected.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There is no hypothesis testing for this trial.

7.3 PLANNED ANALYSES

Safety and efficacy analyses will be based on all treated patients who have received any idarucizumab from a vial. For different efficacy, PK, or PD endpoints, the number of evaluable patients may be different. Details of patient set analysed will be specified in the TSAP. Analysis of safety and efficacy endpoints will be descriptive in nature. The efficacy analysis for reversal will also exclude patients with a pre-dose coagulation test value below the ULN. Baseline will be defined as the last available measurement before dosing of idarucizumab (pre-dose). Details regarding the definitions of important protocol violations will be provided in the TSAP.

7.3.1 Primary endpoint analyses

There is no primary efficacy endpoint. The primary safety endpoint is defined in section 5.1.1.

Occurrence of drug-related adverse events (including immune reactions) and all-cause mortality during the trial (from the start of dosing until 30 days after the end of dosing) will be reported.

Potential specific risks that could be caused by ADA, such as local injection site reactions, systemic hypersensitivity, including anaphylaxis or immune complex disease, are considered as immune reactions, and will be assessed clinically and reported descriptively.

As to summary of other adverse events, refer to section 7.3.4.

7.3.2 Secondary endpoint analyses

Percent change from baseline of coagulation tests (dTT and ECT) at 30 minutes post-dose will be summarized descriptively.

Time to achieve complete reversal and duration of complete reversal of dabigatran effects sustained at 24 hours post-dose based on coagulation tests (dTT and ECT) will be reported by listing the reversal values at planned time points and using flags to show whether complete reversal is achieved.

For Group A patients only, the cessation of bleeding will be reported using a binary outcome (Yes/No) descriptively.
Bleeding status and other clinical conditions that may contribute to bleeding (Group A patients only) during the trial will be reported descriptively.

Development of treatment-emergent ADA with cross reactivity to idarucizumab at 30 days post-dose of idarucizumab will be summarized using a binary outcome (Yes/No) descriptively.

7.3.4 Safety analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Parameters to be evaluated for safety are described in section 5.3. Details will be included in the TSAP.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All AEs will be classified according to the following trial periods: screening, on-treatment, and post-treatment. All AEs with an onset date/time after the 1st vial of trial medication up to one day after the last administration of trial 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. Frequency, severity, and causal relationship of all AEs (including bleeding) in the on-treatment period will be tabulated in total by system organ class and preferred term after coding accordingly to the current version of the MedDRA. AEs in the screening and post-treatment period will be listed.

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

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Pharmacokinetic and pharmacodynamic parameters in this trial will be evaluated descriptively as feasible and appropriate, and calculated according to the BI standards. For ADA, positivity at different time points and titer value will be considered. If necessary, further analyses will be specified in the TSAP.

7.4 INTERIM ANALYSIS

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. However, missing or incomplete AE dates will be imputed according to BI standards.

Handling of missing PK data will generally be performed according to the BI standards. Drug concentration data identified with below the lower limit of quantification (BLQ) 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 Trial Clinical Pharmacokineticist (TCPK) and described in the CTR.

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 upper limit of quantification (ALQ) will be reported. For calculation of reversal of the anticoagulation effect, ALQ values may be replaced by 500s. In that case ALQ values will be discussed on an individual basis within the trial team (including TCM, Trial Biomarker Analyst (TBMA), TCPK and Trial Statistician (TSTAT) and decisions will be documented in the CTR. There are no rules for evaluation. BLQ values as well as pharmacodynamic data identified with no sample available (NOS), no valid result (NOR), and not analysed (NOA) will not be considered.

7.6 RANDOMISATION

This trial has a single treatment group without randomisation.

7.7 DETERMINATION OF SAMPLE SIZE

The design of this trial (including the definition of endpoints and sample size) has been agreed with the European Medicines Agency's Paediatric Committee.

Sample size (approximately 5 patients) is determined based on feasibility.

8 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

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 and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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, and also 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 (and/or the patient's legally accepted representative) and assent (if applicable) according to ICH / GCP and to the regulatory and legal requirements of the participating country. However, due to the need for urgent care in these patients collection of medical history and other standard of care information up to the time of consenting must be provided as part of the study screening procedures and will be collected on the eCRF. 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 and/or the patient's legally accepted representative."

The Investigator must give a full explanation to trial patients (and/or the patient's legally accepted representative as appropriate) based on the patient information form. A language

understandable to the patient (and/or the patient's legally accepted representative as appropriate) should be chosen, technical terms and expressions avoided, if possible. The patient (and/or the patient's legally accepted representative) must be given sufficient time to consider participation in the trial (if feasible in this emergent situation). The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient (and/or the patient's legally accepted representative as appropriate) 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.

Where permitted by local regulatory body and approved by local Ethics Committee an adjusted Informed Consent procedure may be used due to the nature of the emergent medical condition of the patient (e.g. verbal informed consent followed by written informed consent by patient and/or patient's legally accepted representative).

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

Electronic Case Report Forms for individual patients will be provided by the sponsor. 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 subject. 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 eCRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the subject 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 and/or the patient's legally accepted representative, documented in their medical records, would be acceptable.

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 eCRF, data must be derived from source documents, for example:

- Patient identification: gender, date or 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).
- ECG results (original or copies of printouts).
- 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 on-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 on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF 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). The CRA and auditor may review all eCRFs 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 ICH 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 the national or local requirements (whatever is longer) valid at the time of the end of the trial.

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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

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.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial. **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 Suspected Unexpected Serious Adverse Reactions (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. The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10 APPENDICES

10.1 SAFETY AND OTHER CLINICAL LABORATORY EVALUATIONS

Standard safety lab panel may include when feasible parameters as described in section 5.3.3.

Estimated Glomerular Filtration Rate (eGFR) for children should be based on the Schwartz formula. This employs serum creatinine (mg/dL), the child's height (cm) and a constant to estimate the glomerular filtration rate:

eGFR (Schwartz) = (0.41 x Height in cm) / Serum Creatinine in mg/dL

Conversion from conventional unit to SI unit:

Conventional unit	Conversion Factor	SI Unit
mg/mL	88.4	µmol/L

10.2 TIME SCHEDULE FOR BLOOD SAMPLING

Blood volumes to be collected for central lab parameters and local safety lab measurements will depend on available tube sizes and age of the patient as specified in Table 10.2.: 1 and Table 10.2: 2. The sponsor may decide on other tubes sizes, if necessary. In such case total blood volume of the blood sampling may differ.

Cross reporting of lab results might be applied (across studies 1160.106, 1160.108 and this trial) in order not to increase the blood volume required for analysis.

Pre-dose and between vials sampling: central blood sampling for pharmacodynamic biomarkers (dTT, ECT, aPTT, TT), pharmacokinetics (dabigatran and idarucizumab concentration) will occur immediately prior to administration of each vial of idarucizumab. Blood sampling for idarucizumab ADA will only occur prior to vial 1 administration.

Post-dose sampling: central blood sampling for pharmacodynamic biomarkers (dTT, ECT, aPTT, TT), pharmacokinetics (dabigatran and idarucizumab concentrations) will be collected at 30 minutes (± 10 minutes), 4 hours (± 30 minutes), 12 hours (± 1 hour) and 24 hours (± 2 hours) post-dose. Blood sampling for idarucizumab ADA will occur 30 days (+7 days) post-dose.

In Table 10.2.: 1, general required blood volumes are indicated for age category < 6 years of age. For children < 6 years of age, available tube sizes for central lab parameters are 1.2 mL, and 2.7 mL EDTA monovettes and 1.4 mL Na Citrate monovettes. For all central lab parameters and local safety lab measurements about 29 to 37 mL blood will be required during the trial.

In Table 10.2.: 2, general required blood volumes are indicated for age category ≥ 6 years of age. For children ≥ 6 years of age, available tube sizes for central lab parameters are 3.0 mL

EDTA vacutainers and 2.7 mL Na Citrate vacutainers. For all central lab parameters and local safety lab measurements about 43 to 49 mL blood will be required during the trial.

All efforts should be made to use the lowest amount of blood per sample as technically possible by using special paediatric collection systems (R10-4556; R10-4959). Blood sampling for this trial and for dabigatran trial 1160.106 or 1160.108 should not exceed the maximum blood volume limits recommended by the European Commission (R10-4959) nor the maximum specified in local guidelines (if applicable), i.e. blood loss should not exceed 3% of the total blood volume (TBV) over four weeks and should not exceed 1% of the TBV at any single time.

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children. Refer to appendix 10.3 for several reduced blood draw schedules.

All invasive procedures in this trial must be performed only by qualified and experienced health care professionals/physicians with paediatric expertise, with limited attempts to draw blood and/or establish an intravenous (IV) line based on Investigator's judgement.
Prior to venipuncture, a topical (percutaneous) analgesia to reduce pain associated with venipuncture, e.g. amethocaine gel or lidocaine-prilocaine (Emla) cream should be applied on the skin. This should be done according to standard paediatric procedures, and may be omitted only in patients who explicitly refuse it.

Table 10.2: 1 Blood draw schedule (patients < 6 years of age)

		Time	EDTA*	Na Citrate**	Local Safety Lab***	Total blood volume
Visit 1	1	Screening			~ 2 to 6 mL	~ 2 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	2.7 mL	1.4 mL		4.1 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2	2.7 mL	1.4 mL		4.1 mL
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	2.7 mL	1.4 mL		4.1 mL
	5	4 hours (± 30 minutes)	2.7 mL	1.4 mL		4.1 mL
	6	12 hours (± 1 hour)	2.7 mL	1.4 mL		4.1 mL
Visit 3	7	24 hours (± 2 hours)	2.7 mL	1.4 mL	~ 2 to 6 mL	~ 6 to 10 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	1.2 mL			1.2 mL
Total blood volume						**~29 to 37 mL**

*EDTA K3 = PK assays, idarucizumab ADA
**Na Citrate = Biomarkers (dTT, ECT, aPTT, TT)
***Amount of mL will depend on tube sizes used by local lab.

Table 10.2: 2 Blood draw schedule (patients ≥ 6 years of age)

		Time	EDTA*	Na Citrate**	Local Safety Lab***	Total blood volume
Visit 1	1	Screening			~ 3 to 6 mL	~ 3 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	3.0 mL	2.7 mL		5.7 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2	3.0 mL	2.7 mL		5.7 mL
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	3.0 mL	2.7 mL		5.7 mL
	5	4 hours (± 30 minutes)	3.0 mL	2.7 mL		5.7 mL
	6	12 hours (± 1 hour)	3.0 mL	2.7 mL		5.7 mL
Visit 3	7	24 hours (± 2 hours)	3.0 mL	2.7 mL	~ 3 to 6 mL	~ 9 to 12 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	3.0 mL			3.0 mL
Total blood volume						**~ 43 to 49 mL**

*EDTA = PK assays, idarucizumab ADA
**Na Citrate = Biomarkers (dTT, ECT, aPTT, TT)
***Amount of mL will depend on tube sizes used by local lab.

10.3 ESTIMATED TOTAL BLOOD VOLUME

The estimated Total Blood Volume (TBV) will depend on age and gender and will be calculated with following formula:

Total Blood Volume = Weight * Average Blood Volume

Table 10.3.1: Approximate (average) blood volume per age category.

Age category	Approximate (average) blood volume (mL/Kg)
Term newborn infant	80 - 90 (85)
Infants	80
Children (> 3 months)	70-80
Adolescents	
women	65
men	75

For children the approximate total blood volume may vary between 70 - 80 mL/Kg. In order to be conservative, 70 mL/Kg will be used to calculate the total blood volume (TBV).

Examples of TBV calculations:

Infant of 1.5 year old, weight 10 Kg:
- Allowed blood loss at any single time (1% of TBV): 8 mL
- Allowed blood loss over four weeks (3% of TBV): 24 mL

Child of 12 years old, weight 45 Kg:
- Allowed blood loss at any single time (1% of TBV): 31.5 mL
- Allowed blood loss over four weeks (3% of TBV): 94.5 mL

Adolescent (male) of 15 years old, weight 60 Kg:
- Allowed blood loss at any single time (1% of TBV): 45 mL
- Allowed blood loss over four weeks (3% of TBV): 135 mL

Blood sampling could be withheld or reduced per Investigator's judgement, e.g. if limited by blood volume, bleeding and/or distress considerations especially in very young children.

If blood sampling is reduced, central lab parameters will be analysed in a priority order as indicated below:

1) Sum dabigatran pre-dose (baseline)
2) All coagulation biomarkers pre-dose, 30 minutes and 24 hours post-dose
3) Idarucizumab ADA pre-dose and 30 days post-dose
4) PK idarucizumab at time points pre-dose; 30 minutes and 24 hours post-dose
5) All coagulation biomarkers at time points prior vial 2, 4 hours and 12 hours post-dose
6) PK idarucizumab at time points prior vial 2, 4 hours and 12 hours post-dose

7) Unbound sum dabigatran at all time points as noted in Flow Chart

In below tables a few scenarios are displayed if collected blood volumes are limited.

Table 10.3: 1 Reduced blood draw schedule (patients < 6 years of age):
Maximal **29 mL** central lab/local safety blood draw (e.g. no EDTA blood collection prior vial 2, 4 hours and 12 hours post-dose; i.e. no measurement of unbound sum dabigatran and no PK idarucizumab prior vial 2, 4 hours and 12 hours post-dose)

		Time	EDTA	Na Citrate	Local Safety Lab	Total blood volume
Visit 1	1	Screening			~ 2 to 6 mL	~ 2 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	2.7 mL	1.4 mL		4.1 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2		1.4 mL		1.4 mL
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	2.7 mL	1.4 mL		4.1 mL
	5	4 hours (± 30 minutes)		1.4 mL		1.4 mL
	6	12 hours (± 1 hour)		1.4 mL		1.4 mL
Visit 3	7	24 hours (± 2 hours)	2.7 mL	1.4 mL	~ 2 to 6 mL	~ 6 to 10 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	1.2 mL			1.2 mL
Total blood volume						**~21 to 29 mL**

Table 10.3: 2 Reduced blood draw schedule (patients < 6 years of age):

Maximal **25 mL** central lab/local safety blood draw (e.g. no blood collection prior vial 2, 4 hours and 12 hours post-dose; i.e. no measurement of biomarkers, unbound sum dabigatran and no PK idarucizumab prior vial 2, 4 hours and 12 hours post-dose)

		Time	EDTA	Na Citrate	Local Safety Lab	Total blood volume
Visit 1	1	Screening			~ 2 to 6 mL	~ 2 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	2.7 mL	1.4 mL		4.1 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2				
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	2.7 mL	1.4 mL		4.1 mL
	5	4 hours (± 30 minutes)				
	6	12 hours (± 1 hour)				
Visit 3	7	24 hours (± 2 hours)	2.7 mL	1.4 mL	~ 2 to 6 mL	~ 6 to 10 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	1.2 mL			1.2 mL
Total blood volume						**~17 to 25 mL**

Table 10.3: 3 Reduced blood draw schedule (patients ≥ 6 years of age):

Maximal **40 mL** central lab/local safety blood draw (e.g. no EDTA blood collection prior vial 2, 4 hours and 12 hours post-dose; i.e. no measurement of unbound sum dabigatran and no PK idarucizumab prior vial 2, 4 hours and 12 hours post-dose)

		Time	EDTA	Na Citrate	Local Safety Lab	Total blood volume
Visit 1	1	Screening			~ 3 to 6 mL	~ 3 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	3.0 mL	2.7 mL		5.7 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2		2.7 mL		2.7 mL
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	3.0 mL	2.7 mL		5.7 mL
	5	4 hours (± 30 minutes)		2.7 mL		2.7 mL
	6	12 hours (± 1 hour)		2.7 mL		2.7 mL
Visit 3	7	24 hours (± 2 hours)	3.0 mL	2.7 mL	~ 3 to 6 mL	~ 9 to 12 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	3.0 mL			3.0 mL
Total blood volume						**~ 34 to 40 mL**

Table 10.3: 4 Reduced blood draw schedule (patients ≥ 6 years of age):

Maximal **32 mL** central lab/local safety blood draw (e.g. no blood collection prior vial 2, 4 hours and 12 hours post-dose; i.e. no measurement of biomarkers, unbound sum dabigatran and no PK idarucizumab prior vial 2, 4 hours and 12 hours post-dose)

		Time	EDTA	Na Citrate	Local Safety Lab	Total blood volume
Visit 1	1	Screening			~ 3 to 6 mL	~ 3 to 6 mL
Visit 2.1	2	Baseline (just prior vial 1)	3.0 mL	2.7 mL		5.7 mL
Administer Idarucizumab Vial 1						
Visit 2.2	3	Just prior vial 2				
Administer Idarucizumab Vial 2						
Visit 2.2	4	30 minutes (± 10 minutes)	3.0 mL	2.7 mL		5.7 mL
	5	4 hours (± 30 minutes)				
	6	12 hours (± 1 hour)				
Visit 3	7	24 hours (± 2 hours)	3.0 mL	2.7 mL	~ 3 to 6 mL	~ 9 to 12 mL
Visit 4	8	Day 7 (± 3 days)				
Visit 5	9	Day 30 (+ 7 days)	3.0 mL			3.0 mL
Total blood volume						**~ 26 to 32 mL**

11 DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

Number of global amendment		
Date of CTP revision		
EudraCT 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 – 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

Document Number: c08884404 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol

Title: Single dose, open label, uncontrolled, safety trial of intravenous administration of idarucizumab to paediatric patients enrolled from ongoing phase IIb/III clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Trial Clinical Monitor		08 Feb 2016 10:59 CET
Approval-Biostatistics		08 Feb 2016 22:42 CET
Approval-Therapeutic Area		09 Feb 2016 08:15 CET
Author-Pharmacokinetics		09 Feb 2016 13:54 CET
Approval-Team Member Medicine		09 Feb 2016 14:53 CET
Verification-Paper Signature Completion		09 Feb 2016 15:24 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed