Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

	Document Number:	**c02286986-03**
BI Trial No.:	1321.6	
BI Investigational Products:	Idarucizumab	
Title:	Open label Phase I trial in healthy Chinese male and female volunteers to investigate pharmacokinetics and pharmacodynamics of idarucizumab to reverse dabigatran anticoagulant activity	
Lay Title:	Study to evaluate the safety, pharmacokinetics and pharmacodynamics of idarucizumab (BI 655075) administered alone or with dabigatran etexilate in Chinese healthy subjects	
Clinical Phase:	I	
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator :	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised protocol (based on global amendment 1))	
Version and Date:	Version: 2.0	Date: 17 Mar 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not Applicable	
Name of active ingredient:		Idarucizumab	
Protocol date: 20 Oct 2016	**Trial number:** 1321.6		**Revision date:** 17 Mar 2017

Title of trial:	Open label Phase I trial in healthy Chinese male and female volunteers to investigate pharmacokinetics and pharmacodynamics of idarucizumab to reverse dabigatran anticoagulant activity
Principal Investigator:	[redacted]
Trial sites:	Single centre [redacted]
Clinical phase:	I
Objectives:	To investigate pharmacokinetic and pharmacodynamic of idarucizumab administered at or close to the steady state of dabigatran
Methodology:	Open label, single centre
No. of patients:	12
total entered:	12
each treatment:	12 subjects (approximately sex ratio: 1:1)
Diagnosis :	Not Applicable
Main criteria for inclusion:	age ≥18 and ≤45 years, Body weight≥50 kg , BMI range: ≥19 and <24 kg/m^2
Test products:	a) Idarucizumab (50 mg/mL in buffer solution for infusion) b) Dabigatran etexilate (110 mg capsules); only as NIMP
dose:	a) 2 short infusions of 2500 mg each 15minutes apart administered at or close to the steady state of dabigatran; b) 220 mg b.i.d

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not Applicable	
Name of active ingredient:		Idarucizumab	
Protocol date: 20 Oct 2016	**Trial number:** 1321.6		**Revision date:** 17 Mar 2017

mode of administration:	a) Intravenous infusion b) Oral
Comparator products:	Not applicable
dose:	Not applicable
mode of administration:	Not applicable
Duration of treatment:	a) 1 day (2 short infusions of 2500 mg each 15 minutes apart) b) 3 days twice daily (b.i.d.) with a single dose on day 4 (2 times at intervals of 3 days)
Endpoints	The following pharmacokinetic (PK) parameters will be determined as primary endpoints; For idarucizumab: C_{max}, $AUC_{0-\infty}$, Ae_{0-72} The following pharmacodynamic (PD) parameters will be determined as primary endpoints; For dTT: $AUEC_{above,\ 2-12}$ on day 4 and day 11 The following pharmacokinetic (PK) parameters will be determined as secondary endpoints; For sum dabigatran: $Ae_{0-74,ss}$ on day 4 and day 11 For unbound sum dabigatran: AUC on day 4 and day 11 [redacted]
Safety criteria:	Adverse events, laboratory tests (including haematology, clinical chemistry, urinalysis, coagulation parameters and ADA), vital signs (BP, PR, body temperature), 12-lead ECG, and local tolerability.
Statistical methods:	Descriptive statistics for safety, PD and PK endpoints will be calculated.

FLOW CHART 1

Trial Period	Visit	Day	Informed consent	In-/Exclusion Criteria	Dabigatran Administration	Administration of idarucizumab	Vital signs	12-lead ECG	pO2 -monitoring	Laboratory / Urinalysis	Physical examination	Blood sampling for PD[7]	Blood sampling for PK of Dabigatran[7]	Blood sampling for PK of idarucizumab[7]	Urine Collection for PK	Pregnancy Testing[9]	ADA[8]	Hospitalization	Adverse events / Concomitant med.
Scr.	1	-28 to -2	X	X			X[1]	X		X[2,3]	X[5]					X			▲
Treatment period	2	-1					X	X		X[3]	X	X						▲	
		1		X	X		X	X			X	X	X		X		X		
		2			X		X	X											
		3			X		X	X											
		4			X		X	X		X	X	X	X		X				
		5					X	X			X	X	X		X				
		6					X	X				X	X		X			X	
		7					X	X				X	X		X				
		8			X		X	X		X	X								X
		9			X		X	X											
		10			X		X	X											
		11		X	X	X	X[1]	X	X	X	X[6]	X	X	X	X				
		12					X	X		X[3]	X	X	X	X	X				
		13					X	X		X[3,4]	X	X	X	X	X				
		14					X	X		X[3]	X[6]	X	X	X	X			▼	▼
EOT	3	16 to 24					X	X		X[3]	X[6]					X	X		
FU1	4	39 to 45															X		
FU2	5	102 to 108															X		▼

1. Body temperature inclusive
2. Protein electrophoresis, lipase, amylase, hormone, drug and virus screening only at screen
3. Urinalysis including α1-microglobulin, albumin and IgG
4. Urinalysis only
5. At the screening including subject information, demographics, relevant medical history, concomitant medication
6. Local tolerability inclusive.
7. PK and PD sampling times may be adapted based on information obtained during trial conduct
8. ADA (anti-idarucizumab Antibodies) samples will be taken at baseline, EOT, FU1 and FU2.
9. Urine pregnancy test required for all women of child bearing potential. Pregnancy testing is one indicator of pregnancy. Changes in a subject's menstrual cycle, that may indicate pregnancy must also be considered and a further pregnancy test can be taken if the Investigator feels it to be appropriate.

FLOW CHART 2

Part 1: Planned timetable for Treatment period (2 short infusions 15 minutes apart administered at or close to the steady state of dabigatran)

Visit	Day	Planned Time[1] [h:min]	Actual daytime [h:min]	Dabigatran administration	Administration of idarucizumab	Vital signs	12-lead ECG	pO2 -monitoring	Laboratory / Urinalysis	Physical examination	Blood sampling for PD[4,5]	Blood sampling for PK of Dabigatran[5]	Blood sampling for PK of idarucizumab[5]	Urine Collection for PK*	Pregnancy Testing	ADA[6]	Adverse events / Concomitant med.
2	-1					X	X		X[3]	X	X						▲
	1	0:00	7:00	X		X[2]	X[2]			X[2]	X[2]	X[2]		X[2]		X[2]	
		12:00	19:00	X													
	2	24:00	7:00	X		X[2]											
		36:00	19:00	X													
	3	48:00	7:00	X		X[2]	X[2]										
		60:00	19:00	X													
	4	72:00	7:00	X		X[2]	X[2]		X[2]	X[2]	X[2]	X[2]		═			
		73:00	8:00								X	X		═			
		74:00	9:00								X	X		═			
		74:30	9:30								X	X		═			
		75:00	10:00								X	X		═			
		76:00	11:00								X	X		═			
		78:00	13:00								X	X		═			
		80:00	15:00								X	X		═			
		82:00	17:00											═			
		84:00	19:00								X	X		═			
		86:00	21:00											═			
	5	90:00	1:00								X	X		═			
		98:00	9:00			X				X	X	X		═			
	6	122:00	9:00			X					X	X		═			
	7	146:00	9:00			X	X				X	X		═			
	8	168:00	7:00	X		X[2]	X[2]		X[2]	X[2]							
		180:00	19:00	X													
	9	192:00	7:00	X		X[2]											
		204:00	19:00	X													
	10	216:00	7:00	X		X[2]	X[2]										
		228:00	19:00	X													▼

*: Urine sampling for PK relative to morning administration: pre-dose on Day 1, 0–2 h, 2–6 h, 6–12 h, 12–14 h, 14–26 h , 26–50 h , 50–74 h on Day 4-7

FLOW CHART 2

Part 2: Planned timetable for Treatment and End of Study period (2 short infusions 15 minutes apart administered at or close to the steady state of dabigatran)

Visit	Day	Planned Time[1] [h:min]	Actual daytime [h:min]	Dabigatran administration	Administration of idarucizumab	Vital signs	12-lead ECG	pO2 -monitoring	Laboratory / Urinalysis	Physical examination	Blood sampling for PD[4,5]	Blood sampling for PK of Dabigatran[5]	Blood sampling for PK of idarucizumab[5]	Urine Collection for PK**	Pregnancy Testing	ADA[6]	Adverse events / Concomitant med.
2	11	240:00	7:00	X					X[2,3]	X	X[2]	X[2]		═══			▲
		241:00	8:00								X	X		═══			═══
		241:55	8:55		-X-	X[2,7]	X[2]	X[2]		X[2]	X[2]	X[2]	X[2]	═══			═══
		242:00	9:00		-X-	X	X	X			X	X	X	═══			═══
		242:05	9:05		-X-	X	X	X			X	X	X	═══			═══
		242:15	9:15		-X-	X[2,7]	X[2]	X[2]	X[3,8]	X[2]	X[2]	X[2]	X[2]	═══			═══
		242:20	9:20		-X-	X	X	X			X	X	X	═══			═══
		242:22	9:22										X	═══			═══
		242:30	9:30			X	X	X					X	═══			═══
		242:50	9:50			X	X	X					X	═══			═══
		243:20	10:20			X[7]	X	X		X	X	X	X	═══			═══
		244:00	11:00			X[7]	X	X	X[3,8]	X	X	X	X	═══			═══
		245:00	12:00			X	X						X	═══			═══
		246:00	13:00			X[7]	X		X[3]	X	X	X	X	═══			═══
		248:00	15:00			X	X				X	X	X	═══			═══
		250:00	17:00											═══			═══
		252:00	19:00								X	X	X	═══			═══
		254:00	21:00			X[7]	X		X[3,8]		X	X	X	═══			═══
	12	266:00	9:00			X	X		X[3]	X	X	X	X	═══			═══
	13	290:00	9:00			X	X		X[3,8]	X	X	X	X	═══			═══
	14	314:00	9:00			X	X		X[3]	X[9]	X	X	X	═══			═══
3	16 to 24					X	X		X[3]	X[9]					X	X	▼

**:Urine sampling on Day 11 relative to the end of the first idarucizumab infusion: -2 h–(-5) min, -5 min–4 h, 4–10 h, 10–12 h, 12–24 h, 24–48 h, 48–72 h on Day 11–14

1. On the first dabigatran administration basis
2. Predose
3. Urinalysis including α1 microglobulin, albumin and IgG
4. PD includes for each sampling point: Hemoclot® (dTT), aPTT, TT and ECT
5. PK and PD sampling times may be adapted based on information obtained during trial conduct.
6. ADA (anti-idarucizumab Antibodies) samples will be taken at baseline, EOT, FU1 and FU2 after idarucizumab administration.
7. Body temperature inclusive
8. Urinalysis only
9. Local tolerability inclusive.

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ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
Ae_{t1-t2}	amount of the analyte excreted in urine over the time interval t_1-t_2.
ALT	alanine transaminase (SGPT)
[redacted]	[redacted]
AST	aspartate transaminase (SGOT)
AUC_{t1-t2}	area under the concentration-time curve of the analyte in plasma over the time interval t_1 - t_2
$AUC_{0-\infty}$	area under the concentration-time curve of the analyte in plasma / urine over the time interval from 0 extrapolated to infinity
AUEC	area under the effect curve
BI	Boehringer Ingelheim
AUECabove, t1-t2	area after subtraction of baseline area from area under the effect curve above over the time interval from t1 to t2
b.i.d.	bis in die (twice daily administration)
BLQ	below the limit of quantification
BMI	body mass index (weight divided by height squared)
BP	blood pressure
BT	body temperature
CK	creatinine kinase
[redacted]	[redacted]
C_{max}	maximum measured concentration of the analyte in plasma
CML	local clinical monitor
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organisation
CRP	C-reactive protein
CTMF	clinical trial master file
CTP	clinical trial protocol
[redacted]	[redacted]
dTT	diluted thrombin time
ECG	electrocardiogram
eCRF	electronic case report form
[redacted]	[redacted]
EDTA	ethylendiaminetetraaceticacid
e.g.	example given
EOT	end of treatment
F	absolute bioavailability factor
FAS	full analysis set

FcRn	neonatal Fc receptor
[redacted]	[redacted]
FDA	Food and Drug Administration
FU	follow-up (FU1 (visit 4), FU2 (visit 5))
g	gram(s) (for description of mass); gravity (description of centrifugation)
GCP	Good Clinical Practice
gCV	geometric coefficient of variation
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Committee on Harmonisation
INR	international normalised ratio
IRB	institutional review board
ISF	investigator site file
iv	intravenous
kDa	kilodalton
[redacted]	[redacted]
ln	natural logarithm
MedDRA	Medical Dictionary for Drug Regulatory Affairs
[redacted]	[redacted]
NBI	Nippon Boehringer Ingelheim
NIMP	non-investigational medicinal product
nM	nanomolar
NOA	not analyzed
NOP	no peak detectable
NOR	no valid result
NOS	no sample available
OPU	operative unit
PAS	periodic acid-schiff
PD	pharmacodynamic
pH	pondus hydrogenii; negative logarithm of the hydrogen ion concentration
PK	pharmacokinetic(s)
po	per os (oral)
PR	Pulse rate
QT	time between the start of the Q-wave and the end of the T-wave in an ECG
RDC	remote data capture
REP	residual effect period
RR	respiratory rate
SAE	serious adverse event
Scr.	screening
SmPC	Summary of Product Characteristics
SOP	standard operating procedure
ss	(at) steady state
τ	dosing interval

[redacted]	[redacted]
TCM	trial clinical monitor
TCPK	trial clinical pharmacokineticist
TdP	torsades de points
[redacted]	[redacted]
TSAP	trial statistical analysis plan
TSH	thyroid stimulating hormone
TSTAT	trial statistician
[redacted]	[redacted]
ULN	upper limit of normal
[redacted]	[redacted]

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Anticoagulation therapy is a mainstay of treatment and prevention of thrombosis in different clinical settings. Several new oral anticoagulants such as dabigatran have been developed, with efficacy comparable to or better than Vitamin K antagonists such as warfarin. However, for all anticoagulants bleeding, including life-threatening or fatal bleeding remains a major side effect.

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)

The estimated bleeding rates from post-marketing surveillance are not in excess of the rates of bleeding seen in the RE-LY trial, it highlights the need for an additional method of reversing the anticoagulant effect of dabigatran in subjects who bleed. 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.
Dabigatran associated bleeding is currently managed with standard supportive care. Temporary discontinuation of dabigatran should occur if there is active pathological bleeding. Because dabigatran is primarily excreted unchanged via the kidneys, maintenance of adequate diuresis is important. Dabigatran is dialyzable, removing approximately 50 - 60% of dabigatran in plasma over 4 hours; clinical data supporting this approach are limited. In addition, haemodialysis is not available at all hospitals, it may not be possible in some patients and usually requires some time to be initiated. Surgical haemostasis, transfusion of fresh frozen plasma or red blood cells can also be considered. There is some experimental evidence to support the use of 3-factor, activated prothrombin complex concentrates (PCCs, containing coagulation factors II, IX or X) or recombinant Factor VIIa (rFVIIa); however, their usefulness in clinical settings has not been established. In cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used, administration of platelet concentrates can be considered. Measurement of aPTT, ECT or diluted thrombin time (dTT) or other assays currently under investigation, may help guide therapy (P11-04551).

Some anticoagulants/antithrombotics have a specific antidote that can be used in emergency situations where rapid reversal of anticoagulation is required. For example, protamine sulphate is used for the heparins. Vitamin K isn't a specific antidote for warfarin as it takes a minimum of six hours to counteract the anticoagulation effect and does not directly antagonize the effect of the anticoagulant but only facilitates synthesis of coagulation factors.. The new oral anticoagulant agents currently lack a specific antidote. An ideal antidote would

be safe, specific, immediately effective, and easy to administer. Idarucizumab is being developed as a specific neutralizing agent for dabigatran which is easily available and can rapidly and safely reverse the anticoagulant effect of dabigatran in patients that require this in emergency situations.

1.2 DRUG PROFILE

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

Idarucizumab

Drug Substance and Drug Product

Idarucizumab is a humanized Fab molecule derived from a IgG1 isotype molecule, directed against dabigatran, a direct thrombin inhibitor.

The molecule is composed of the light chain (LC, amino acids 1 - 219) and the heavy chain fragment (HC, amino acids 1 - 225), covalently linked together by one disulfide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain.

The theoretical average molecular weight of the Fab molecule is 47.8 kDa.
Idarucizumab is expressed in Chinese hamster ovary (CHO) cells. It is manufactured using standard mammalian cell culture techniques, followed by a series of protein purification steps including several chromatography steps, as well as steps for removal and inactivation of potential viruses.

The drug product, idarucizumab solution for injection/infusion 50 mg/mL is used as solution or concentrate for injection. It will be administered intravenously (i.v.).

Idarucizumab has been approved in 2015 in the United States, the European Union and NewZealand. Marketing experience is limited but to date no new safety signals have been identified.

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

In an in vitro study, idarucizumab binds to dabigatran with a high affinity (Kd) of 2.1 pM, >300-fold more potent than the binding affinity of dabigatran for thrombin. The calculated in vitro dissociation half-life of the idarucizumab-dabigatran complex was approximately 260 hours. Idarucizumab potently inhibited the anticoagulant activity of dabigatran (7 nM) with an IC_{50} of 2.4 nM. It also showed the same effect on dabigatran metabolite (glucuronate conjugate). This indicates that idarucizumab potently and specifically binds dabigatran and neutralizes its anticoagulant activity.

In vivo examination of the idarucizumab's reversal effect on dabigatran-induced anticoagulant activity and effects on haemorrhage were performed in rats. A single bolus of idarucizumab at an equimolar dose completely reversed the anticoagulant activity of dabigatran to baseline within one minute after administration. There was an approximately 2-fold prolongation in bleeding time in dabigatran (30 mg/kg) induced haemorrhage model, which was reversed after 5 minutes to baseline levels and remained reversed over the entire 2 hours measurement period with idarucizumab (single intravenous bolus of 0.69 µmol/kg (33 mg/kg)).

Safety pharmacology studies have demonstrated no effects on the respiratory, CNS, or cardiovascular systems (U12-3330-01, U12-3327-01, U12-3328-01).

Local tolerance to the idarucizumab clinical formulation was assessed by measurement of potential hemolytic effect in vitro and by microscopic examination of injection sites in

monkeys receiving two doses of idarucizumab intravenously (U12-3289-01). Idarucizumab did not cause hemolysis of human blood. In the two-dose GLP study in Rhesus monkeys, Microscopic examination of injection sites revealed no evidence of a idarucizumab formulation related effect (U12-3328-01).

A tissue cross-reactivity studies was conducted to assess the potential for idarucizumab to bind to rat, monkey, and normal human 35 different tissues. No tissue binding was observed in either species (U12-3331-01).

Toxicology

Toxicity studies for idarucizumab have been designed and performed to support Phase I single-dose clinical trials.

A 4-week GLP study with daily intravenous administration of idarucizumab to rat at 500 mg/kg/day showed no adverse responses during drug phase or following a 4-week recovery phase. In rats treated with idarucizumab, a decrease in plasma urea and creatinine was observed in a dose-related manner, but no correlating histopathologic changes were observed in kidneys. These decreases were reversed in females during the 4-week recovery phase, but urea levels in male rats remained somewhat below concurrent control levels at the end of recovery, albeit within normal limits for rats. The cause for the observed decreased urea and creatinine is unknown, but as no concurrent adverse changes were observed these changes are judged of no biological relevance. Electrolyte levels in idarucizumab-treated rats remained within normal limits (U12-3327-01).

In the two-dose GLP toxicity study, 26 monkeys were exposed to idarucizumab by daily administration of idarucizumab over 2 days. Twenty of those 26 animals received 500 mg/kg idarucizumab, with half also receiving pre-treatment with dabigatran etexilate. Of those 20 animals, 8 continued into a 14-day recovery phase, with 4/8 receiving idarucizumab after dabigatran etexilate. One of the 20 monkeys receiving 500 mg/kg idarucizumab, i.e., 500/12 mg/kg idarucizumab/dabigatran etexilate Monkey #157, began to exhibit evidence of renal dysfunction approximately 24 hours after the second dose of idarucizumab, which increased

in severity over the 14 day recovery period. In recovery phase, this monkey displayed signs indicative of poor health. None of the 19 other animals treated with 500 mg/kg idarucizumab, with or without dabigatran etexilate, showed a similar pattern of changes, nor did any of the six animals that received 150/12 mg/kg idarucizumab/dabigatran etexilate. The monkey #157 exhibited increases in plasma urea and creatinine and decreases in plasma electrolytes. The plasma chemistry changes suggest an adverse effect on renal tubular function. However, renal microscopic changes were limited to dilated cortical tubules and PAS-positive material in tubule lumens, neither of which are considered explanatory of the plasma chemistry or urinalysis findings.
A relationship of the above effects to dabigatran exposure was excluded for Monkey#157 as no similar changes were observed in a 52-week study in Rhesus monkeys with dabigatran etexilate exposed to similar or higher dabigatran and sum dabigatran levels (U05-1557).

A follow-up study repeated the dose regimen utilized in the previous monkey study. No adverse changes were observed in monkeys treated with 500/12 mg/kg idarucizumab/dabigatran etexilate or 500 mg/kg idarucizumab. Therefore, the adverse effects observed in the first study were not reproducible.

At the end of a PK/PD study in Rhesus monkeys, one animal collapsed during the third occasion of a idarucizumab infusion, the remaining seven animals appeared normal. This animal had previously received idarucizumab on two other occasions, spaced 1 week apart. The third scheduled infusion occurred 22 days after the second infusion. The timing of idarucizumab administrations may have sensitized the animals to idarucizumab, which is not unexpected as idarucizumab is a humanized Fab. The nature of the response is under investigation, but is suggestive of a Type I hypersensitivity reaction.

In both species, there was no difference in idarucizumab maximum plasma levels or exposure between sexes or in rats between single-dose or repeated daily administration for 4 weeks.

Non-clinical Pharmacokinetics

In both rats and monkeys, the product exhibited biphasic plasma concentration-time profiles (initial half-life <30 minutes (in which approximately95% of total dose is included) and terminal half-life 4-7 h, MRT 0.57 hours in rats and 1.1 hours in monkeys). Approximately 10-20% of idarucizumab dose was directly excreted into urine. Based on precedence in the literature, the expectation is that idarucizumab not cleared in the urine is cleared by catabolism. Pharmacokinetics of idarucizumab were linear with dose, and volume of distribution was small (approximately 0.06 L/kg, only slightly larger than the plasma volume).

The volume of distribution of dabigatran was smaller in rats treated with idarucizumab (0.180 L/kg) than in rats without dabigatran treatment (0.561 L/kg), consistent with redistribution of dabigatran from tissue to plasma after idarucizumab dosing. Idarucizumab did not change the urinary excretion of dabigatran in the rat or sum dabigatran (dabigatran plus its glucuronides) in the monkey.
Idarucizumab reversed the anticoagulant effect of dabigatran and its glucuronides as assessed by diluted thrombin time (dTT), [redacted] measurements in the monkey when idarucizumab molar concentration was in excess or the concentration difference between sum dabigatran and idarucizumab was small. At sufficiently higher dose levels of idarucizumab, complete reversal of dabigatran's anticoagulant activity was maintained over 24h.

Clinical Trials

The clinical pharmacology of idarucizumab has been investigated in 3 Phase I trials and one ongoing Phase III trial in patients, summarized below. The Phase I trials are as follows: one study in healthy male volunteers (1321.1), one study in healthy male Japanese volunteers (1321.5) and one study in healthy, male and female, mid-aged or elderly subjects as well as subjects with mild or moderate renal impairment (1321.2). These studies provide proof of concept as well as dose finding and therefore, at the same time, serve the purpose of a Phase II study.

The first-in-man trial 1321.1 (U13-1773) was performed according to a double-blind, randomized, single rising dose and placebo-controlled (within dose groups) design in young

healthy male volunteers. The primary objectives were to investigate safety, tolerability and pharmacokinetics of single rising intravenous doses of idarucizumab from 20 mg to 8 g over 1 h or from 1 g to 4 g over 5 min, to explore doses of 1 g, 2 g and 4 g of idarucizumab to reverse dabigatran anticoagulant activity in subjects pre-treated with 220 mg DE b.i.d. and to confirm the safety and efficacy of maximum expected dose of idarucizumab (5 g + 2.5 g) in subjects pre-treated with 220 mg DE b.i.d. Idarucizumab was administered around the tmax of dabigatran following the 7th dabigatran dose on day 4.

The Phase Ib study, 1321.2 (c02742738), further assessed the neutralizing effect of idarucizumab on dabigatran plasma levels in volunteers. 1321.2 was a double-blind crossover study versus placebo, with 6 to 8 subjects per group with three dose levels of idarucizumab (1g, 2.5 g, and 5 g). Middle-aged healthy volunteers, elderly subjects (age 65-80 years) and subjects with mild renal impairment (estimated CrCl ≥60 to <90 mL/min) or moderate renal impairment (estimated CrCl≥30 to <60 mL/min) were included. The aim was to investigate safety, tolerability, and the PK of idarucizumab and to confirm an efficacious dose of idarucizumab that reverses dabigatran's anticoagulant activity. With dabigatran plasma levels at steady state after 3 days of dosing 220 or 150 mg DE b.i.d., idarucizumab was administered as either a single i.v. rapid infusion ~2 hours after the single dose of DE on day 4, or two i.v. infusions of 2.5 g, 1 hour apart, with the first infusion starting ~2 h after the last dose of DE.

All subjects underwent two similar study periods in a cross-over fashion, both periods with dabigatran, followed by either idarucizumab or placebo. To explore whether there is an influence of prior idarucizumab treatment on anticoagulation induced by newly administered dabigatran, healthy subjects age 45-64 were given five doses of 220 mg DE b.i.d. starting 24 hours after administration of idarucizumab. Six subjects were also re-treated with DE +idarucizumab 2 months after the first exposure to idarucizumab, to evaluate possible immunogenicity, e.g. formation of ADA. Safety data will be supportive for possible re-exposure to idarucizumab in the patient population.

The first-in-Japanese trial (1321.5 (c03026940) assessed safety, tolerability, and pharmacokinetics of several doses of idarucizumab when administered alone or at dabigatran

steady state in Japanese male volunteers. Similar to study 1321.1 the primary objective of this study is to investigate safety, tolerability and pharmacokinetics of single rising intravenous doses of idarucizumab (Part 1) and to explore a dose of idarucizumab that is effective in reversing dabigatran anticoagulant activity (Part 2).

The Phase III study in patients is ongoing. Study 1321.3 (RE-VERSE AD) is a prospective, uncontrolled, open-label, (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 dministration 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.

Idarucizumab Anti Drug Antibodies (ADA)

Of a total of 145 subjects analyzed, 19 subjects (13.1%) had positive titers at baseline (pre-dose) which tended to persist at the subsequent sampling times at end-of-study, 4 weeks and 3 months follow up. For placebo subjects the incidence of positive titers at baseline was 19.4% (7 of 36). For subjects who received idarucizumab, 11.0% (12 of 109) had positive

titers at baseline. Positive titers before administration of idarucizumab which persist at 4 weeks and 3 months follow up suggest the presence of nonspecific ADA.

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

These data indicate that in healthy volunteers, single doses of idarucizumab ranging from 20 mg to 8000 mg are not associated with the formation of persistent ADA.

Dabigatran

For further details see the latest "Package insert" filed in the ISF.

Dabigatran is a direct thrombin inhibitor, which interacts with the active site in the catalytic domain of the thrombin molecule. Dabigatran etexilate 110 mg and 150 mg capsule has been marketed in China under the trade names Pradaxa® for stroke and systemic embolism prevention in patients with atrial fibrillation.
The PK profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with C_{max} attained within 0.5 and 2.0 hours post administration. After repeated dosing, steady state is reached by day 3 of treatment. There is no accumulation of dabigatran on repeated dosing (U03-1878). The terminal half-life of dabigatran ranged from 12-17 hours on repeated dosing. The average ratios of accumulation observed with dabigatran etexilate 150 mg twice daily were 1.4- and 1.3-fold for the area under the plasma-concentration time curve (AUC) and C_{max}, respectively (U06-3091). About 80% of systemic available dabigatran is eliminated unchanged renally.

Dabigatran plasma concentrations and the PK parameters C_{max} and AUC increased in a dose proportional manner after oral administration of the prodrug dabigatran etexilate and after intravenous infusion of dabigatran (U98-3208-14, P08-05411)

The increases in [redacted] prolongation were dose dependent and closely correlated with dabigatran plasma concentration-time profiles. The maximum effect was observed at the time of maximum plasma concentration of dabigatran indicating that thrombin inhibition by dabigatran is a direct effect linked to the central (plasma) compartment.

[redacted]

Numerous Phase I trials in healthy subjects explored the PK of dabigatran and its potential for drug-drug and drug-food interactions. The safety was investigated with 400 mg up to 3 times daily for multiple dose administration. Safety and tolerability were confirmed up to 200 mg t.i.d. over 7 days in healthy subjects, and no clinically relevant adverse events were detected.

Dabigatran etexilate has been investigated in over 30 Phase I trials, 6 completed Phase II trials, and 6 completed Phase III trials. Diarrhea, dyspepsia, and nausea were the most frequently reported gastro-intestinal adverse events. Transaminase elevations <2x ULN were common (27 to 31%). The commonly observed adverse events were bleeding, as would be expected with any anticoagulant. However, dabigatran treatment was associated with lower rates of life-threatening major bleeds including lower rates of haemorrhage stroke and intracranial haemorrhage compared to warfarin in RE-LY (U09-3249-02).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is intended to assess pharmacokinetics and pharmacodynamics of idarucizumab when administered at the steady state of dabigatran in Chinese male and female volunteers via intravenous of idarucizumab. The dose of idarucizumab is selected based on Caucasian (1321.2) and Japanese (1321.5) trial, in order to provide the basis for clinical development for the emergency situations when the anticoagulant activity of dabigatran should be rapidly and safely reversed. The results of this trial can be properly compared with the results of 1321.2 and 1321.5 at same dose.

Furthermore, this trial is designed to achieve the plasma concentration of dabigatran at steady state and the maximum plasma concentration of dabigatran similar to concentrations obtained after administration of dabigatran etexilate 150 mg b.i.d to the patient population (including Chinese patients) with non-valvular atrial fibrillation of RE-LY (U10-2017-01). It is estimated to be close to the ranges of concentrations observed in patients of RE-LY by administration of dabigatran etexilate 220 mg b.i.d. to healthy volunteers by means of modelling techniques (U12-3431). Therefore one of the secondary objectives of this trial is to explore the PD effects of idarucizumab administered at or close to the steady state of dabigatran.

2.2 TRIAL OBJECTIVES

The primary objective of the trial is to investigate the pharmacokinetics and pharmacodynamics of idarucizumab in Chinese healthy male and female subjects following intravenous administration of 2500 mg idarucizumab followed by 2500 mg idarucizumab with 15 minutes interval when administered at or close to the steady state of dabigatran.

Another objective of this trial is to explore the effect idarucizumab on the PK and PD parameters of dabigatran.

Additionally safety, PK and PD parameters between healthy Japanese, Caucasian and Chinese volunteers will be compared and discussed.

2.3 BENEFIT - RISK ASSESSMENT

There is no therapeutic benefit to subjects from taking part in this trial. However, the results of the trial will be beneficial to the wider patient's community treated with dabigatran. The ability to safely reverse dabigatran anticoagulant activity in a timely and highly effective fashion in emergency situations would be a major advance for patients and physicians and will further enhance the favourable overall safety profile of dabigatran.

Idarucizumab is a humanized Fab with high binding affinity to dabigatran which will be applied as an intravenous infusion to healthy subjects. Idarucizumab exposure will be limited due to its expected short half-life. Furthermore, clinical data indicate that in healthy subjects, single doses of idarucizumab ranging from 20 mg to 8000 mg are not associated with the formation of persistent ADA.

The molecular weight of the Fab molecule is approximately 47 kDa which is comparable with the human serum albumin (67 kDa). Based on the fact that 4.5 L human blood (7% of the body weight of the 60 kg human) contains approximately 180 g albumin. It is inferred, idarucizumab doses in this trial, infusion of 2500 mg idarucizumab followed by 2500 mg idarucizumab 15 minutes apart would not cause significant changes in oncotic pressure and compromise the osmotic homeostasis.

Based upon preclinical information available to date, healthy subjects in this trial will not be exposed to undue safety risks.

In Phase I trial (1321.1), the administration of 8000 mg as an 1 hour infusion of idarucizumab did not show major concern about the tolerability in 1321.1. Therefore, the tolerable dose level of 1321.1 is much higher than the dose to be used in this trial.
To minimize risk, procedures are defined to evaluate the drug related adverse event caused by the trial drug. And criteria and rules for stopping subject treatment as whole are defined

(Section 3.3.4.1).

During this trial, totally 5000 mg idarucizumab administered at or close to the steady state of dabigatran are planned. The dabigatran etexilate dosing schedule of 220 mg b.i.d. for 3 days + 1 dose on day 4 in healthy subjects is selected to achieve steady-state plasma concentrations similar to those observed in the patient population dosed with 150 mg b.i.d. in RE-LY (Section 4.1.4) (U10-2017-01). In Japanese healthy volunteers, the safety of dabigatran etexilate was confirmed with 300 mg for single dose administration and twice daily 150 mg for multiple dose administration (U06-3091, U06-3420, U05-3334). In Caucasian healthy volunteers, the safety was investigated with 600 mg for single dose administration and 400 mg up to 3 times daily for multiple dose administration. Safety and tolerability were confirmed up to 200 mg t.i.d. (600 mg as a daily dose) (U99-1502, U00-1856, U06-1614-01, U06-1609-01). Additionally, the safety was confirmed with twice daily 225 mg multiple dose administration in patients undergoing an orthopaedic surgery (U04-1195-01). And twice-daily 300 mg multiple-dose administration was tried in patients with atrial fibrillation (U06-1615-02). Even though the risk of bleeding might be increased at a dose of 220 mg twice daily (440 mg as a daily dose) to Chinese healthy volunteers, the possibility of occurrence of severe adverse events is estimated very low. In this trial, the dabigatran etexilate administration alone period is intended to evaluate the tolerability and safety of multiple doses of 220 mg dabigatran etexilate. Subjects safety will be ensured by thorough monitoring including blood coagulation parameters under controlled environments. During in house confinement the subjects will be under medical observation and thoroughly monitored for any adverse events.

Especially, to minimize the risk of bleeding coagulation parameters will be closely monitored in subjects of the trial. Bleeding will be managed with the help of rescue medication, emergency procedures, and additional treatments regarding bleeding events (Section 4.2.1). Administration of trial drug will be immediately stopped in case of any clinically relevant adverse events or reactions. A clinical monitoring up to 24 hours after drug administration will be frequently performed (e.g. vital signs including body temperature, ECG, pO2 monitoring, laboratory tests, local tolerability, and adverse events).

The subjects are carefully monitored by investigator and site staffs through 14 days from initiation of dabigatran etexilate administration to 72 hours after drug administration. This is

expected to cover the period of highest risk / peak effect based on the short half-live of idarucizumab. Close laboratory monitoring of renal function will be performed (creatinine, electrolytes, urea, urinalysis including determination of low molecular weight proteins). Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety, see also Section 5.3.6.1.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will be open label with only 1 dose group.

A total of 12 subjects will participate in the trial.

This trial consists of two periods; the dabigatran etexilate administration alone period is intended to evaluate the safety of multiple doses of 220 mg dabigatran etexilate b.i.d, and in the second period idarucizumab will be administered at or close to steady state of dabigatran and is intended for exploratory PK/PD analysis with the dose (2500 mg followed by 2500 mg).

At the dabigatran etexilate administration alone period, all subjects will receive 220 mg dabigatran etexilate b.i.d. (440 mg daily dose) for 3 days and a single 220 mg dose on day 4 to reach dabigatran or close to steady state.

Following dabigatran etexilate administration alone, after a washout period of 3 days and evaluation of safety 220 mg dabigatran etexilate will be administered twice daily over 3 days (from day 8 to day 10) with a single 220 mg dose on day 11. The dose of idarucizumab (2500 mg followed by 2500 mg is planned) will be administered intravenously approximately 2 hours after the last dabigatran administration.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).
Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to

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

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and 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.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Healthy subjects as trial population are an ideal population since they provide relatively stable physiological, biochemical and hormonal conditions for performing clinical trials. These conditions are the absence of disease-related variations and concomitant medications. Healthy subjects can be tested under standardized conditions and in an environment which allow repeated testing. With regard to the target population, the dose of 2 short infusions of 2500 mg with 15 minutes interval reflects the current clinical dose in phase III (1321.3) (U13-5106-01) and healthy Japanese subjects(1321.5). Furthermore, a safety study of administrations of idarucizumab given at steady state of dabigatran will help to define an appropriate dose for the clinical use.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 12 healthy male and female subjects (approximately sex ratio 1:1) will be entered in the trial (see Section 7.6).

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

3.3.1 Main diagnosis for trial entry

The healthy Chinese male and female subject who meets the inclusion criteria and does not conflict with exclusion criteria.

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

Healthy males and females according to the following criteria:

1. Age ≥18 and Age ≤45 years at screening
2. Healthy male and female based upon a complete medical history, including vital signs (BP, PR, and BT), 12-lead ECG and clinical laboratory tests. Women of childbearing potential[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.
3. Body weight≥50 kg with BMI range ≥19.0 and <24.0 kg/m^2 at Visit 1.
4. Signed and dated written informed consent in accordance with GCP and local legislation prior to admission to the trial.

3.3.3 Exclusion criteria

1. Any finding of the medical examination (including BP, PR, BT and ECG) is deviating from normal and judged as clinically relevant by the investigator
2. Any evidence of a clinically relevant concomitant disease according to investigator's clinical judgement
3. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders

[1] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

4. Surgery of the gastrointestinal tract that could interfere with kinetics of the trial medication (except appendectomy)
5. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
6. History of relevant orthostatic hypotension, fainting spells or blackouts.
7. Chronic or relevant acute infections
8. History of relevant allergy/hypersensitivity (including allergy to drug or its excipients) or immune system disease
9. Intake of drugs with a long half-life (> 24 hours) within at least 30 days or less than 10 half-lives of the respective drug prior to first trial drug administration
10. Within 10 days prior to administration of trial medication, use of drugs that might reasonably influence the results of the trial or that might prolong the QT/QTc interval.
11. Participation in another trial with investigational drug administration within 60 days prior to first trial drug administration
12. Smoker (> 10 cigarettes or > 3 cigars or > 3 pipes/day)
13. Inability to refrain from smoking during hospitalization
14. Alcohol abuse (consumption of more than 20 g per day: e.g., 1 middle-sized bottles of beer, 1 gou [equivalent to 180 mL] of sake))
15. Drug abuse or positive drug screening
16. Blood donation (400 mL whole blood donation within 12 weeks, 200 mL whole blood donation or blood component donation within 4 weeks) prior to first trial drug administration
17. Intention to perform excessive physical activities within one week prior to first trial drug administration or during the trial
18. Any laboratory values outside the reference range that are of clinical relevance according to investigator's clinical judgement
19. Inability to comply with dietary regimen of trial site
20. A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTcF interval >450 ms)
21. A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
22. Positive HIV test result at screening examination

23. Positive testing for Hepatitis B Antigen and/or a positive Hepatitis C antibody test result at screening examination
24. Subjects considered unsuitable for inclusion by the investigator, e.g. are unable to understand and comply with trial requirements, or have any condition which in the opinion of the investigator would not allow safe participation in the trial.
25. Subjects who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until 12 weeks after the trial completion. Acceptable methods of contraception comprises barrier contraception and a medically accepted contraceptive method for the female (intra-uterine device with spermicide. hormonal contraceptive since at least 8 weeks)
26. History or evidence of blood dyscrasia, haemorrhagic diathesis, severe thrombocytopenia, cerebrovascular haemorrhage, bleeding tendencies associated with active ulceration or overt bleeding of gastrointestinal, respiratory or genitourinary tract or any disease or condition with haemorrhagic tendencies (e.g. cerebral aneurysm, dissecting aorta, CNS trauma, retinopathy, nephrolithiasis)
27. Abnormal values for PT, aPTT and thrombocytes considered by the investigator or one of the co-investigators to be clinically relevant
28. Creatinine and estimated glomerular filtration rate (GFR) outside the normal range
29. Evidence of proteinuria
30. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

A record of all subjects screened, in- or excluded, will be maintained.
For trial restrictions, see Section 4.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

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

An individual subject is to be withdrawn from the trial if:

□□The patient withdraws consent, without the need to justify the decision

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

- The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The subject can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases)
- If a subject becomes pregnant during the trial the investigational drug will be stopped, the subject will be discontinued from the trial medication and the subject will be followed up until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up on the outcome of the pregnancy. Please see Section 5.3.6.2.
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

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

For all subjects the reason for withdrawal (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.
If a subject is withdrawn from the trial prior to administration of any trial medication, the data of this subject will not be entered in the trial database and not be reported. If a subject discontinues or withdraws from the trial thereafter, this will be documented and the reason for withdrawal will be recorded in the clinical report forms (CRFs), the data will be included in the trial database and will be reported. At the time of discontinuation a complete end-of-treatment evaluation will be performed if possible and the information will be recorded in the CRFs. Those withdrawals will be discussed in the final report of the trial.

In case that not all subjects complete the dose level, the TCM together with the TCPK and the TSTAT decide if and how many subjects will be replaced. Each subject will have a unique subject identification number including replacing subjects.

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

Early discontinuation of the trial by the investigator

1. dosing will be stopped immediately in case if clinically relevant allergic reaction/ hypersensitivity (e.g. fever > 39°C, dyspnoea, rush) occurs which needs medical intervention
2. due to occurrence of signs of any intercurrent illness during the dosing
3. due to an adverse event, sufficiently severe to contraindicate continuing the trial
4. occurrence of a major bleeding, or sustained minor bleedings which cannot be controlled with the local haemostasis, any other bleeding event considered clinically relevant by the investigator, or positive haemocult test during the trial

The investigator can be guided by the criteria above, but may discontinue subjects at any time based on his/her clinical judgment.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Idarucizumab drug product (50 mg/mL) is manufactured at: Boehringer Ingelheim Pharma GmbH & Co KG

4.1.1 Identity of the Investigational Medicinal Products

The investigational product idarucizumab and NIMP dabigatran will be supplied by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. The compositions of these drugs are detailed in Table 4.1.1: 1 and Table 4.1.1:2.

Table 4.1.1: 1 Investigational product

Substance:	Idarucizumab(BI 655075)
Pharmaceutical formulation:	50 mL solution for iv infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg/mL
Posology	2 short infusions of 2500 mg each 15 minutes apart
Route of administration:	intravenous (iv) infusion

Table 4.1.1: 2 Non-Investigational product

Substance:	Dabigatran etexilate
Pharmaceutical formulation:	capsules
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	110 mg
Posology	3 days 220 mg twice daily (b.i.d.) with a single dose 220mg on day 4
Route of administration:	oral (po)

4.1.2 Selection of doses in the trial

Idarucizumab

The dose of idarucizumab applied in this trial was selected as follows:

Idarucizumab doses are estimated based on the equimolar neutralization of the body load of the target molecule (dabigatran) after multiple 220 mg b.i.d. dosing.

The absolute bioavailability of dabigatran is on average 6.5%啊 after oral dosing of dabigatran etexilate (U09-2347-01) and an accumulation of 1.7-fold is assumed after b.i.d. dosing (U06-3420). A 220 mg dose dabigatran etexilate is equivalent to about 165 mg of dabigatran. The amount of dabigatran absorbed into the body is: 165 mg* 6.5% = 10.7 mg. The estimated dabigatran body load after 220 mg dabigatran etexilate b.i.d. multiple dosing will be 10.7 mg *1.7 = 18.2 mg.

18.2 mg would be equivalent to 0.0386 mmol (38.6 µmol). 38.6 µmol idarucizumab are equal to 1.844 g = 1844 mg (MW of idarucizumab = 47782 Da).Therefore, for 100% neutralization a dose of about 2000 mg idarucizumab is required.

Meanwhile, higher doses of idarucizumab may be needed to neutralize higher dabigatran exposures. The initial half-life of idarucizumab, which exhibited biphasic plasma concentration-time profile, is only about 45 minutes based on the completed trial (1321.1). In contrast, the re-distribution of dabigatran from peripheral tissues may continue for several hours. Administration of additional doses of idarucizumab over time is hypothesized to allow binding of dabigatran that re-distributes from tissues into the plasma, as compared to administration of the entire dose at once. Consequently, investigating idarucizumab 2500 mg intravenous infusion over 5 minutes followed by idarucizumab 2500 mg intravenous infusion over 5 minutes 15 minutes apart has been implemented in other studies across this clinical program. Therefore, the dose of idarucizumab in this trial was chosen to test the intended therapeutic dose at the time of planning of this study and to compare with the Phase I trial (1321.5) data and other studies with idarucizumab.

Dabigatran etexilate

The doses of dabigatran etexilate applied in this trial were selected as follows:

When dabigatran etexilate is administered to healthy adults at a dose of 220 mg twice daily for 3 days and once at a dose of 220 mg in a fasting state two hours before administration of this drug on Day 4, the plasma concentration of dabigatran will reach at steady state. The plasma concentrations of dabigatran at steady state achieved in this trial are comparable with the maximum plasma concentration of dabigatran after administration of 150 mg twice daily to the subject population in the phase III global study conducted in subjects with non-valvular atrial fibrillation including Japanese (U09-3249-02).
Therefore, the dabigatran etexilate dosing schedule of 220 mg b.i.d. for 3 days + 1 dose on day 4 in healthy subjects is selected. The dosing schedule was adapted in the Phase I trial (1321.1).

4.1.3 Method of assigning patients to treatment groups

Only 1 dose group is planned in this trial, and it is unnecessary to randomize subject.

The allocation process of subjects will be performed on day 1 prior to study drug administration. Once a subject number has been assigned, it cannot be reassigned to any other subject.

4.1.4 Drug assignment and administration of doses for each patient

The drug product, idarucizumab (50 mg/mL) is administered solution for infusion without dilution. Trial medication will be filled into an infusion solution bag and will be used for iv infusion.

The treatments to be evaluated are as outlined in Table 4.1.4: 1 below.

The trial medication will be prepared according to the preparation instructions by authorized personnel at the trial site. For the correct preparation of idarucizumab intravenous solutions, see the ISF.

Table 4.1.4: 1 Dose group

Dose group	**1**
Dose [mg]	2500 + 2500
Total volume of idarucizumab in infusion bag to be prepared [mL]	150
Infusion volume of idarucizumab to be applied [mL]	50 + 50
Infusion time [min]	5 + 5
Infusion volume rate [mL/h]	600 + 600

For the dose group, following an overnight fast of at least 8 hours for the morning dose, and at least 2 hours for the evening dose, dabigatran etexilate will be administered with 240 mL of water in the sitting position under supervision of the investigator or designee. BI655075 will be administered under supervision of the investigator or designee approximately 2 hours after the last dabigatran administration on day 11.

- Subjects are not allowed to lie down during the 2 hours following dabigatran etexilate administration (i.e. no declination of the upper body of more than 45 degrees from upright posture) unless supine position is required for clinical assessments. They are not allowed to sleep.
- On day 4: from 1 hour before dabigatran etexilate intake until 4 hours post-dose, liquid intake is restricted to the fluid administered with the drug and additional 240 mL of water at approximately 1hour 30 minutes and 4 hours post-dose, respectively (mandatory for all subjects). From 4 hours post-dose until 24 hours post-dose, water intake is restricted to 3000 mL.

- On day 11: from 1 hour before dabigatran etexilate intake until 4 hours post-dose, liquid intake is restricted to the fluid administered with the drug and additional 240 mL of water at approximately 1hour 30 minutes (before BI655075 administration) and 4 hours post-dose, respectively (mandatory for all subjects). From 4 hours post-dose until 24 hours post-dose, water intake is restricted to 3000 mL.

Standardised meals will be served at 2, 5 and 9 hours following morning drug administration on days 1, 2, 3, 8, 9, 10 and at 4 hours and 9 hours post morning dose on days 4, 11. Additionally, snacks will be served 2 hours after the evening intake of dabigatran on days 1-3, 8-10 and 13 hours post dose on day 11.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This open-label, Phrase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis).

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.

The trial medication must be stored securely, e.g. in a locked cupboard or at a pharmacy. It may only be dispensed to trial subjects according to the protocol by authorised personnel at the trial site.

All unused medication must be returned to the sponsor. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

4.1.8 Drug accountability

The Investigator < and/or > Pharmacist < and/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

The Investigator < and/or > Pharmacist < and/or > investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, 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 subjects. The Investigator / Pharmacist / investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP and

reconcile all investigational products received from the sponsor. At the time of return to the sponsor< and/or >appointed CRO, the Investigator / Pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

Primarily, no concomitant therapy will be allowed. However, in case of AEs in need of treatment, symptomatic therapy according to the judgement of the investigator will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the electronic case report forms (eCRFs).
In the case of AEs the subjects will be treated as necessary and, if required, kept under constant supervision at the trial site or transferred to hospital until such time that all the results of the evaluations have returned to a medically acceptable level.
It is of major importance for group treated with dabigatran etexilate to monitor the subjects for bleeding events.

In case of unexpected minor bleeding local haemostasis has to be initiated as medically required and careful monitoring of the subject is needed. For minor bleedings a watchful waiting approach is generally appropriate.

If a subject experiences a major bleed, the trial medication should be stopped and the bleeding treated according to local practice. This will generally involve coagulation testing (aPTT, TT, fibrinogen, platelet count), transfusion support, and surgical haemostasis as indicated.

According to the experience with bleeding events in other circumstances, some general recommendations can be given:

The administration of aminocaproic acid (a potent inhibitor of fibrinolysis) and of vasopressin analogues (leading to increased circulating levels of pro-coagulant factor VIII and von Willebrand factor) can be useful in certain circumstances of bleeding events. In preclinical trials with direct thrombin inhibitors the administration of recombinant factor VIIa or Activated prothrombin complex concentrates (e.g., FEIBA) has been found to be useful and can also be considered. Consideration may be given to the use of fresh frozen plasma and it may also be possible to remove dabigatran by haemodialysis.

The use of these agents may be discussed in case of an overdose of dabigatran. Due to the unpredictable effect of these therapies a careful balance against potential untoward effects has to be done on an individual basis.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Use of concomitant medications which affects the clotting parameters or is known to have PK interaction with dabigatran (e.g. acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole or aspirin/dipyridamole, warfarin, other Vitamin K-dependent anticoagulants, or known P-gp inhibitors/inducers) is not permitted since the combination of any of these agents with dabigatran may increase the risk of bleeding. Non-steroidal anti-inflammatory drugs (NSAIDs) and systemic corticosteroids are restricted, but may be used if clinically indicated.

4.2.2.2 Restrictions on diet and life style

Subjects should abstain from alcoholic beverages for at least 48 hours prior to first trial drug administration and until EOT visit examination and from smoking during the whole domicile period.

Methylxanthine-containing drinks or foods (coffee, tea, cola, energy drinks, chocolate, etc.) are not permitted 24 hours preceding the administration of trial medication and until the end

of plasma and urine PK sampling. Citrus fruits, in particular grapefruits and Seville oranges (sour or bitter oranges), and their juices as well as products containing St. John's wort (Hypericum perforatum) are not permitted 5 days before the administration of trial medication and until the end of plasma and urine PK sampling of the respective visit.
The subjects are instructed not to use any additional concomitant drug or undergo any medical treatment or any surgical procedure 14 days prior to, during and until EOT visit without having informed the investigator or his/her deputy.

While admitted to the trial site the subjects are restricted from consuming any foods or drinks other than those provided by the site staff.

On all days when laboratory sampling is planned, subjects will appear after an overnight fast, however, at least for 6 hours on day -1 (1 day prior to the first trial day). Subjects must not expose themselves to direct sun light or use artificial solaria during participation in the clinical trial.

Excessive physical activity should be avoided during the course of the trial (competitive sport etc.).

In order to minimize the risk of acquiring a potential bleeding, all subjects planned to be enrolled in the groups with dabigatran treatment, will be reminded of the following precautions:

- Be alert to early signs of bleeding such as occurring of blushes, pain in the abdomen, lower back or side. If any of these symptoms occur, subjects have to get in touch with the trial physician immediately
- Take care to avoid cuts or other injuries. Be especially careful when using knives, razors, nail clippers and other sharp objects. Check with the trial physician for the best ways to clean the teeth and mouth without injuring the gums.

4.2.2.3 Restrictions regarding women of childbearing potential

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

4.3 TREATMENT COMPLIANCE

Subjects who are non-compliant, e.g., they do not appear for treatment or violate the restrictions, may be withdrawn from the trial and the eCRF will be completed accordingly (for further procedures see Section 3.3.4.1). If subject withdraws during Visit 2 (after administration of the trial drug), a complete post-examination will be performed. Compliance will be assured by administration of all trial medication under supervision of the investigator or designee. The measured plasma concentrations and/or urinary excretion will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

A total amount of approximately 328 mL blood will plan to be taken per subject until EOT visit of the trial. In addition to that, 4 mL blood will plan to be taken per subject for ADA measurements at FU1 and FU2 after idarucizumab administration.

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoints

The following pharmacokinetic parameters will be determined as Primary endpoints, if feasible:For idarucizumab: C_{max}, $AUC_{0-\infty}$, Ae_{0-72}

The following pharmacodynamic parameters will be determined as Primary endpoints:
For dTT: $AUEC_{above,2-12}$ on day 4 and day 11

5.1.2 Secondary Endpoints

The following pharmacokinetic parameters will be determined as secondary endpoints, if feasible:

For sum dabigatran: $Ae_{0-74,ss}$ on day 4 and day 11

For unbound sum dabigatran: $AUC_{2-12,ss}$ on day 4 and day 11

[redacted]

5.2 ASSESSMENT OF EFFICACY

Efficacy measurements will not be performed.

The PD parameters listed in Section 5.1.1 and 5.1.3 will be used to explore the effect of idarucizumab on coagulation parameters.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

Physical examination (for the time points see Flow Chart) will include an examination of general appearance, skin, lungs, heart, abdomen, lymph nodes, extremities and basic nervous system evaluation.

Information about the physical examination must be present in the source documentation at the trial site. Significant findings made after the start of trial drug which meet the definition of an AE must be recorded as the AE in eCRF.

5.3.2 Vital Signs

Systolic and diastolic blood pressure (BP) as well as pulse rate (PR) will be measured after at least 5 minutes of rest in the supine position. All recordings shall be made using the same BP recording instrument on the same arm (see Flow Chart for time points). Body temperature (BT) will be measured at the time points described in the Flow Chart. All measurements will be evaluated and signed by the investigator or designee. Any abnormalities considered significant by the investigator will be carefully monitored and reported as AEs and if necessary, the subject will be removed from the trial and medically treated. A description of the overall assessment, i.e. normal or abnormal (clinically significant or clinically not significant) will be made. All measurements will be documented and kept at the site as the source data.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed at the trial site.

A total amount of approximately 80 mL blood will plan to be taken per subject during the whole course of the trial for laboratory parameters. This amount may be exceeded if unscheduled (additional) monitoring of laboratory results is warranted.

The respective reference ranges will be provided in the ISF (see Flow Chart for time points of laboratory blood sampling).

Urine sediment will only be done if there is a positive finding on the urinalysis. The tests listed in Table 5.3.3: 1 constitute lab tests adopted in the exclusion criteiria. These tests may be repeated as required. The results will not be included into the report, although the results are filed at the investigator's site as source documents (except for Albumin, IgG, alpha-Microglobulin).

To encourage compliance, a breath alcohol test and urine drug screen will be performed at screening, on admission and may be performed at any time during the trial by the discretion of an investigator or designee. The results will not form part of the report, although the results are filed at the investigator's site as source documents.

Urine protein and urine glucose will be performed qualitative and quantitative measurement. The results of the qualitative analysis will not be included into the report, although the results are filed at the investigator's site as source documents.

Laboratory data will be entered into the eCRF.

Fecal occult blood test will be performed at Screening (Visit 1). Subjects are allowed to collect the specimen in a tube at home and bring the tube at the trial site. The results will not form part of the report, although the results are filed at the investigator's site as source documents.

Pregnancy Testing

A urine pregnancy test will be performed locally on all women of child bearing potential at screening and EOT visits.

Table 5.3.3: 1 Routine laboratory tests

Category	Test name
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Red Blood Cell Count/Erythrocytes Reticulocyte Count White Blood Cells/Leucocytes Platelet Count/Thrombocytes
Diff. Automatic (relative count)	Neutrophils Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Partial Thromboplastin Time (=aPTT) Prothrombin Time (Quick and INR) Fibrinogen
Enzymes	AST/GOT, SGOT ALT/GPT, SGPT Alkaline Phosphatase (AP/ALP) Creatine Kinase (CK) CK-MB if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase[1] Amylase[1]
Hormones[1]	TSH fT3, fT4
Substrates	Glucose Creatinine Bilirubin Total Bilirubin Direct Protein, Total Protein electrophoresis[1] Albumin Alpha-1-Globulin Alpha-2-Globulin Beta-Globulin Gamma-Globulin C-Reactive Protein (CRP) Uric Acid Cholesterol, total Triglycerides
Electrolytes	Calcium Sodium Potassium

Table 5.3.3: 1 Routine laboratory tests (cont.)

Category	Test name
Fecal occult blood test[1, 2]	Blood/Erythrocytes
Urinalysis (Stix)	Urine Nitrite Urine Protein (qualitative[2] and quantitative test) Urine Glucose (qualitative[2] and quantitative test) Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH Urine creatinine[1]
Low molecular weight proteins	Albumin, IgG, Alpha-Microglobulin
Urin-Sediment (microscopic examination) (only if urinalysis [stix] will be positive)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelium Cells Urine Sediment RBC/Erythrocytes Urine Sediment WBC/Leucocytes
Drug Screening (Urine) [1, 2]	Phencyclidine Benzodiazepine Barbiturates Opiates Cocaine Amphetamines Tetrahydro-cannabinol Tricyclic antidepressant
Infectious Serology [1, 2]	Hepatitis B Surface Antigen (qualitative) Hepatitis B HBc Antibody (qualitative) Hepatitis C Antibodies (qualitative) HIV-1 Antibody (preliminary screening) Syphilis test (TP antibody method)

1. Only at screening.
2. Results will not be part of the report.

5.3.4 Electrocardiogram

For the assessment of possible drug induced electrocardiographic changes and/or safety monitoring 12 lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a ECG machine.

In order to assure high quality recordings at comparable resting phases of the subjects the subjects will be laid down in supine position for at least 5 minutes prior to each of the intended time points (see Flow Chart) in order to achieve a stable heart rate at rest. The site personnel will be instructed to assure a relaxed and quiet environment and that all subjects are at complete rest during the recordings.

Triple of ECGs 1 to 3 minutes apart will be recorded prior to idarucizumab administration on day 11 only.

In order not to confuse ECG recording, PK/PD samples should be taken after performing the ECG.

ECG recordings at planned time points may be repeated for quality reasons like alternating current artifacts, muscle movements and electrode dislocation. In this case the repeated ECG recordings may be used for the planned analysis.

All locally printed ECGs will be evaluated by the trial investigator or designee. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator.

Clinically relevant abnormal findings will be reported as adverse events. Any ECG abnormalities will be carefully monitored and if necessary the subject will be removed from the trial and medically treated.

For the inclusion/exclusion of a subject and for the assessment of cardiac safety during the trial the QT and QTc values generated by the ECG machines or their manual corrections by the investigators will be used.

5.3.5 Other safety parameters

PO2 monitoring

The PO2 monitoring will be evaluated by the investigator and any clinically relevant findings will be reported as an AE in eCRF. The results will not form part of the report, although the results are filed at the investigator's site as source documents.

Local tolerability

Local tolerability (for the time points see Flow Chart) will be assessed by the investigator or designee according to "swelling","induration", "heat", "redness", "pain", or other findings. Findings during the trial should be documented as adverse events.

Anti-drug antibody (ADA)

Anti-drug antibody (ADA) will be collected at baseline, EOT, FU1 and FU2.

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 subject 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 subject 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 subject 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 events, 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 adverseevent.

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.

The following are considered as AESIs:

Hepatic injury

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

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

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity 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 study drug treatment continues or remains unchanged.

5.3.6.2 Adverse event collection and reporting

AE Collection

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 CRF(s) by the Investigator:

- From signing the informed consent onwards until follow up visit 1 ((28-34 days after last trial medication application):
  - all AEs (non-serious and serious) and all AESIs.
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After follow up visit 1 until the individual subject's end of trial:
  - all related SAEs and all related AESIs.

- After the individual subject's end of the trial:
  the Investigator does not need to actively monitor the subject for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.

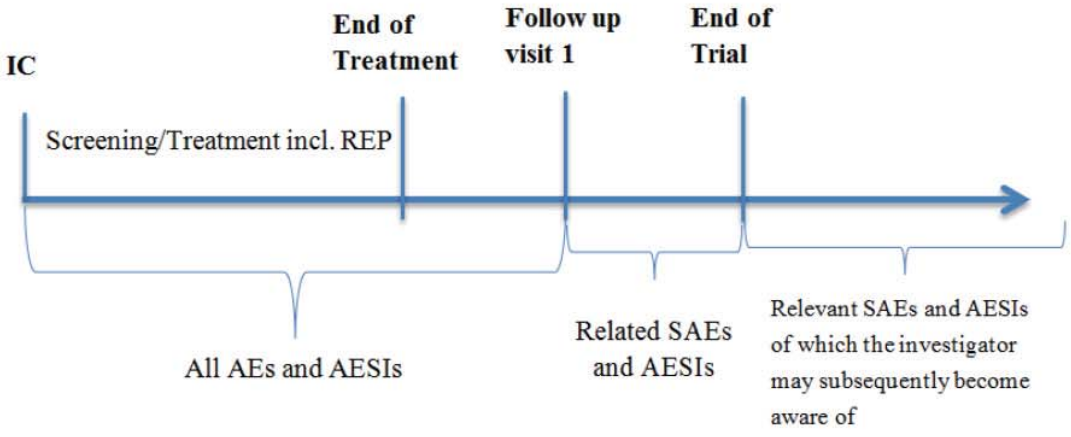

Figure 5.3.6.2: 1 Safety events collection and reporting

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 until the end of treatment visit will be considered as on treatment. Please see Section 7.3.4. Events which occurred after the end of treatment visit will be considered as post treatment events.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP).

The following should also be recorded as an (S)AE in the CRF 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 subject'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 subject 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 and/or AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and exact clock time of po administration, start and end of infusion time as well as of pharmacokinetic sampling times have to be recorded.

5.4.1 Assessment of Pharmacokinetics

The following PK parameters will be determined for idarucizumab, if feasible:

- C_{max} (maximum measured concentration of the analyte in plasma)
- [redacted]
- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

The following PK parameters will be determined for idarucizumab, if feasible:

- Ae_{t1-t2} (amount of analyte eliminated in urine from the time point t_1 to time point t_2)

[redacted]

In addition, the following dose normalised parameters will be calculated for idarucizumab:

Additional pharmacokinetic parameter for idarucizumab may be calculated as appropriate.
In addition, the following PK parameters will be determined for unconjugated dabigatran, sum dabigatran, unbound dabigatran, unbound sum dabigatran and active dabigatran (calculated from dTT (Hemoclot® DTI assay), if feasible:

- $AUC_{t1\text{-}t2,ss}$ (area under the concentration-time curve of the analyte in plasma over the time interval from t1 to t2 at steady state)

Further, the following pre-dose concentrations will be determined for sum dabigatran, if feasible:

- [redacted]

Further, the following PK parameter will be determined for unconjugated dabigatran and sum dabigatran, if feasible:

- $Ae_{t1\text{-}t2,ss}$ (amount of analyte eliminated in urine at steady state from the time point t_1 to time point t_2)

In addition, for unbound dabigatran, unbound sum dabigatran

- [redacted]
- [redacted]

Further, the following PK parameter will be determined for active dabigatran, if feasible:

- [redacted]

Additional pharmacokinetic parameters for unconjugated dabigatran, sum dabigatran, unbound dabigatran, unbound sum dabigatran and active dabigatran may be calculated as appropriate.
Urine parameters will only be calculated as feasible for the analytes measured in urine, i.e. idarucizumab, as well as unconjugated and sum dabigatran.

5.4.2 Methods of sample collection

5.4.2.1 Plasma sampling for pharmacokinetic analysis

A total amount of approximately 156 mL blood will plan to be taken per subject during the whole course of the trial for pharmacokinetic purposes.
Quantification of idarucizumab

For quantification of idarucizumab plasma concentrations, 2 mL of blood will be collected from a forearm vein in an EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at time points indicated in the Flow Chart. For the early time points after drug

administration, the pharmacokinetic samples should be obtained from the forearm not used in the idarucizumab infusion. Immediately after blood sampling, the EDTA-anticoagulated blood samples will be inverted several times and then transferred into an ice bath until centrifugation.

The EDTA-anticoagulated blood samples will be centrifuged within 30 minutes after collection (intermittent storage in ice water or on ice). Centrifugation will last for about 10 minutes at 2000-4000 x g at 4-8°C. EDTA plasma will be transferred into two polypropylene sample vials (at least 0.5 mL for primary sample and remaining for the second). The sample tube labels should list at least the following information: trial number, subject number, visit, planned time, idarucizumab, plasma, and aliquot number.

Until shipment on dry ice to the bioanalytical laboratory, the plasma samples will be stored in an upright position at about -70°C or below. Initially, only aliquot 1 will be sent to the bioanalytical lab. Aliquot 2 will be shipped only after acknowledgement of receipt of the first aliquot.
After completion of the trial the plasma samples may be used for further methodological investigations, e.g., for stability testing. However, only data related to the analyte will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 3 years after the final trial report has been signed.

Quantification of dabigatran
For quantification of analyte plasma concentrations, 4 mL of blood will be taken from a forearm vein in a EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube. Relative time points are given in the trial Flow Chart. Immediately after blood sampling the drawing tubes will be inverted several times and transferred into an ice bath until centrifugation. The EDTA-anticoagulated blood samples will be centrifuged within 30 minutes after collection (intermittent storage in ice water or on ice). Centrifugation will last for about 10 minutes at 2000-4000 x g at 4-8°C. EDTA plasma will be transferred into 3 polypropylene sample vials (aliquot 1 should contain 300 µL, aliquot 2 should contain 1100 µL and aliquot 3 should contain the remaining plasma). The sample tube labels should list at

least the following information: trial number, subject number, visit, planned time, Dabigatran (or abbreviation thereof), plasma, and aliquot number.

Plasma samples will be frozen within 60 minutes after blood withdrawal in an upright position at about -70°C or below. Until shipment on dry ice to the bioanalytical laboratory, the plasma samples will be stored at about -70°C or below at the trial site and stored at the analytical laboratory at approximately -70°C or below until analysis. Aliquots 1 and 2 will be shipped together whereas aliquot 3 serves as a back-up and will be shipped separately.

5.4.2.2 Urine sampling for pharmacokinetic analysis

Quantification of idarucizumab and dabigatran (unconjugated and sum dabigatran)

A blank urine sample will be collected prior to drug administration on day 1 and four aliquots of 2 mL each retained to check for analytical interference.

All urine voided during the sampling intervals listed in the Flow Chart will be collected in polyethylene (PE) containers and stored refrigerated (4-8°C) during the collection interval Subjects have to empty their bladder at the end of each sampling interval. The consumption of water (100 mL) some time before the end of a planned urine fraction will support a timed urine collection. Therefore, subjects will be advised to drink at least 100 mL before the end of urine sampling interval. The urine weight/volume (weight will be set equal to volume, i.e. 1 kg = 1 L, without correction for specific gravity of urine) for each collection interval will be documented and four aliquots of 2 mL (idarucizumab and dabigatran analysis, except for urine samples obtained on day 4 to 7 (only two aliquots needed, as these samples will only be analysed for dabigatran analytes) each will be stored in polypropylene tubes for bioanalytical measurement at about -70°C or below.

Make sure that the urine voided within one collection interval is well mixed before preparing the aliquots. In case more than one collection container was used during a collection interval, the volume of all containers has to be mixed before aliquots are prepared. Mixing should be done by transferring the entire volume of all collection containers for a collection interval into a single PE/PP or glass container, and stirring the mixed fractions for about 1 minute

(manually or using a stir bar etc., device should be either PE/PP/Teflon or glass). The sample tube labels should list at least the following information: trial number, subject number, visit, planned time (interval start - stop), analyte (idarucizumab or dabigatran), matrix (urine) and aliquot number.

Until transfer to the analytical laboratory, the urine samples will be stored at about -70°C or below at the clinical site. The aliquots will be transferred to the analytical laboratories together with the corresponding plasma samples. Two aliquots (primary and back-up) of urine for each collection interval will be shipped to the idarucizumab bioanalytical lab , and remaining two aliquots of urine for each collection interval will be shipped to the dabigatran bioanalytical lab. Primary and back-up aliquots will be shipped separately.
The sampling intervals are detailed in Flow Chart.

5.4.2.3 Plasma sampling for anti-drug antibody (ADA)

For measurements of:
Anti-idarucizumab antibody samples: 2 mL of blood will be collected from a forearm vein in a EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at baseline, EOT FU1, and FU2 after idarucizumab administration. Immediately after blood sampling, the EDTA-anticoagulated blood samples will be inverted several times and then transferred into an ice bath until centrifugation.

The EDTA-anticoagulated blood samples will be centrifuged within 30 minutes after collection (intermittent storage in ice water or on ice). Centrifugation will last for about 10 minutes at 2000-4000 x g at 4-8°C. EDTA plasma will be transferred into two polypropylene sample vials (at least 0.5 mL for primary sample and remaining for the second). The sample tube labels should list at least the following information: trial number, subject number, visit, planned time, ADA-075, plasma, and aliquot number.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g., for stability testing or characterization of ADA. The trial samples will be

discarded after completion of the additional investigations but not later than 3 years after the final trial report has been signed.

5.4.3 Analytical determinations

5.4.3.1 Analytical determination of idarucizumab plasma and urine 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.

[redacted]

For shipment of samples, see the ISF.

5.4.3.2 Analytical determination of dabigatran plasma concentrations

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

[redacted]

The following analyses will be performed:

- "unconjugated" dabigatran = total amount of dabigatran in plasma (samples not hydrolysed i.e. without glucuronide metabolites)
- "sum" dabigatran = total amount of dabigatran in plasma (after sample hydrolysis, i.e. comprising the sum of unconjugated plus glucuronide conjugated dabigatran)
- "unbound" dabigatran = fraction of "unconjugated" dabigatran (after plasma ultrafiltration, i.e. unconjugated dabigatran, that is neither bound to idarucizumab nor to plasma proteins)

- "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)

For shipment of samples, see the ISF.

5.4.3.3 Analytical determination of dabigatran urinary concentrations

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

The following analyses will be performed:

- "unconjugated" dabigatran (samples not hydrolysed i.e. without glucuronide metabolites)
- "sum" dabigatran (after sample hydrolysis, i.e. comprising the sum of unconjugated plus glucuronide conjugated dabigatran)

For shipment of the samples, see the ISF.

5.4.3.4 Analytical determination of anti-drug antibodies (ADA)

Human anti-idarucizumab antibodies will be detected in human plasma samples by a validated bridging ECL method. Samples will be screened for anti-idarucizumab antibodies. Putative positive samples will be subjected to a confirmation assay, and positive samples will also be titered and evaluated for neutralizing antibody activity.

Detailed descriptions of the assays will be available prior to the start of sample analysis.
For shipment of EDTA plasma samples identified to be used for the anti-idarucizumab antibody assay, see the ISF.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

See Section 7.3.5.3 for a description of the planned analysis of PK-PD relationship.

5.5 ASSESSMENT OF BIOMARKERS

Not applicable

5.5.1 Biobanking

Not applicable

5.6 OTHER ASSESSMENTS

A total amount of about 84 mL blood will plan to be taken per subject during the whole course of the trial for pharmacodynamic parameters (see Flow Chart for time points of blood sampling). With the exception of the primary endpoints dTT, all pharmacodynamic parameters are considered exploratory and analytical methods have been validated to fulfill the requirements of the exploratory analyses, 'fit-for-purpose' validation.

5.6.1 Pharmacodynamic endpoints

Measures of pharmacodynamics will comprise the blood coagulation parameters diluted Thrombin time (dTT), [redacted]

Further to the parameters described as Primary endpoints and secondary endpoints in Section 5.1.1and 5.1.2, the following parameters will be determined, if feasible:

[redacted]

In addition for [redacted] and dTT:

- $AUEC_{above,\ t1\text{-}t2}$ on day 4 and day 11

[redacted]

Additional pharmacodynamic parameters may be calculated as appropriate.

5.6.2 Methods of sample collection

Date and exact clock time of pharmacodynamics sampling times have to be recorded. Samples of dTT (Hemoclot® DTI assay), [redacted] in citrated plasma will be analysed at time points as specified in the Flow Chart.

Diluted Thromin Time (dTT, FIIa inhibition), [redacted]

The blood coagulation parameters [redacted] and diluted thrombin time (dTT, Hemoclot® DTI assay) will be investigated.

Approximately 2.7 mL of blood will be collected in Na Citrate collection tubes at time points specified in the Flow Chart. The blood samples will be centrifuged immediately (at least within 30 minutes; blood samples should be kept on ice until centrifugation) at approximately 2500 x g for 20 minutes at approximately 4°C. Plasma will be divided into 6 separate aliquots in appropriately labelled (2 x 100 µL for dTT, 2 x 300 µL for [redacted], and 2 x 150 µL for [redacted] determination) polypropylene vials and frozen immediately at -20°C or below. Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at -20°C or below at the clinical site. Three of 6 aliquots will be shipped to the analytical laboratory for analysis. Three back-up aliquots will be stored at the trial site and sent to an analytical laboratory upon request.

For shipment of the samples, see the ISF.

Left over samples for PD analysis may be used for coagulation assay development and validation purposes (e.g. method comparison or sample stability studies) of additional PD parameters like d-dimer and F1.2. The samples may be analyzed for these parameters, if

available. Left-over samples after these measurements will be stored for a period of 3 years after completion of the trial.

5.6.3 Analytical determinations

Diluted Thrombin Time (dTT, FIIa inhibition), [redacted] will be determined by validated assays at [redacted]

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine PK and PD parameters in an appropriate way.
The PK parameters and measurements outlined in Sections 5.1.1. and 5.4.1 are generally used as measurements to assess drug exposure.

The scheduled measurements are appropriate to monitor drug induced changes in vital signs, standard laboratory values and ECG. These endpoints are standard and accepted for evaluation of safety and tolerability of a drug, and they are widely used in this kind of trials. Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. Time windows are permitted as follows:

- General Physical examination: at screening (2 to 28 days prior to the first trial day) and at the EOT (16 to 24 days).

For planned individual plasma concentration sampling times and urine collection intervals see the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded in eCRF and used for determination of PK parameter.

The designation "before" on trial days refers to the time period of within 2 hours before drug administration (planned time -2:00) (see Flow Chart), i.e. trial measurements and assessments scheduled to occur "before" have to be performed and completed within 2 hours prior to drug administration.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in periods

Screening Period

After the subjects have been informed on the trial, all subjects will have given their written informed consent in accordance with GCP and the local legislation prior to admission to the trial.

For the physical and laboratory examinations during the screening visit, see Sections 5.3, the screening investigations will be performed on 2 to 28 days prior to the first trial drug administration.

Drug and virus screening will be performed (for details see Section 5.3.3).

6.2.2 Treatment periods

Subjects will be institutionalized on day -1. The following investigations will be performed:

- Physical examination including AE questioning
- Clinical laboratory,

Each subject will receive multiple doses of dabigatran etexilate 220 mg b.i.d. from day 1 to 3 with a single dose on day 4 and from day 8 to 10 with a single dose on day 11, 2 doses of idarucizumab will be administered intravenously approximately 1hour 55 minutes and 2 hours 15 minutes after the last dose of dabigatran etexilate on day 11.

Subjects will be kept under close medical surveillance and will stay in the trial site for at least 72 hours after the idarucizumab dose. Subjects will be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee.

The measurements performed during the treatment period are specified under Section 5.3.and in the Flow Chart. For details on time points for all trial procedures, see Flow Chart.

In general, if several measurements including venipuncture are scheduled for the same point of time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiologic parameters.

6.2.3 Follow Up Period and Trial Completion

A physical examination, as well as evaluation of BP, PR, a 12-lead ECG and standard laboratory tests , and assessment of local tolerability will be performed at the EOT visit (within 14 days after last trial drug administration). Trial completion will be at FU2 visit. All clinically significant abnormal values (including laboratory parameters) will be followed up using the appropriate tests until a return to a medically acceptable level is achieved.

EOT, FU1 and FU2 visits will be approximately 10 days, 4 weeks and 12 weeks after idarucizumab dosing respectively, to investigate immunogenicity (ADAs) and collect the AEs. Adverse events will be followed up until FU2 visit or until they have normalised or been sufficiently characterised.

For details and procedures required at EOT, FU1, and FU2 visits, please see Flow Chart.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

Endpoints of this trial are given in Section 5, and the trial design is described in Section 3.1.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. All parameters will be evaluated descriptively.

7.3 PLANNED ANALYSES

All statistical analyses will be based on the treated set.

Treated set:
This subject set includes all subjects who received the investigational drug.

When necessary, PK/PD set may be created for PK/PD analysis, details will be described in the TSAP.

7.3.1 Primary endpoint analyses

For pharmacokinetic, and pharmacodynamic analyses, details are described in Sections 7.3.5.

7.3.2 Secondary endpoint analyses

For safety, pharmacokinetic, and pharmacodynamic analyses, details are described in Sections 7.3.5.

7.3.4 Safety analyses

Safety analyses will be performed based on BI standards. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data. Safety endpoints (adverse events, laboratory parameters and vital signs) will be assigned to the following treatments for analyses based on the AE onset time (concept of treatment emergent AEs) or the planned time of the laboratory parameters and vital signs. the data recorded prior to first intake of dabigatran will be assigned to 'screening', and those between first intake of dabigatran until first idarucizumab intake will be assigned to 'dabigatran period', and those between first intake of idarucizumab until the EOT visit will be assigned to 'dabigatran + treatment', and those between EOT visit until the end of trial (FU2 visit) will be assigned to 'post- treatment', and those after the end of trial visit examination will be assigned to 'post-study'.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. Serious and other significant AEs will be listed separately.

Descriptive statistics of laboratory values and those for the differences from baseline will be calculated. Frequency tables of changes with respect to the reference range between baseline and post-baseline value will also be presented.

Descriptive statistics for vital signs (blood pressure and pulse rate) will be calculated.

Details will be described in the TSAP.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

7.3.5.1 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.4.1 will be calculated according to the Boehringer Ingelheim SOP "Standards and processes for analyses performed

within Clinical Pharmacokinetics/Pharmacodynamics" and given in Appendix 10.1.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, that is, to the same number of decimal places provided in the bioanalytical report.
The following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with 3 significant digits in the clinical trial report.

Pharmacokinetic analyses will be performed using validated software programs, normally. Phoenix Winnonlin (Pharsight®) with applications validated for the respective purpose. Graphs and tables will be generated using validated customised SAS® macros or appropriate graphic software. A reference to the software used, e.g., name, will be indicated in the clinical trial report.

7.3.5.2 Pharmacodynamic analyses

The PD parameters listed in Section 5.6.1 will be calculated according to the Boehringer Ingelheim SOP "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics".

The following descriptive statistics will be calculated as well as for all PD parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of PD marker will be identical with the data format of the respective PD marker. The descriptive statistics of PD parameters will be calculated using the individual

values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with 3 significant digits in the clinical trial report.

For the other parameters of interest [redacted] and dTT (Hemoclot® DTI assay), as well as for [redacted], ratio to baseline will be plotted versus time.

Reversal of dabigatran-mediated anticoagulation will be explored based on return of coagulation measurements into the normal range (i.e. below ULN), where feasible. [redacted]. Similar investigations will be done for [redacted], if feasible. The definition of baseline will be based on pre-dose measurement(s) plus/minus an appropriate tolerance for the respective PD measurement. Details will further be specified in the TSAP.

[redacted]

7.3.5.3 Pharmacokintetic-Phamacodynamic relationship analyses

[redacted]

Details will be further specified in the TSAP.

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

With respect to safety evaluations, it is not planned to impute missing values except for AE dates. These will be imputed according to BI standards.

7.5.2 Plasma concentration - time profiles

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

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

7.5.3 Pharmacokinetic parameters

For the noncompartmental analysis to idarucizumab and dabigatran, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored.

The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit. BLQ values for unbound dabigatran and unbound sum dabigatran data will be handled exceptionally; BLQ values will be replaced by the lower limit of quantification which is defined as 1 ng/mL.

If the predose concentration of the first administration is less than or equal to 5% of C_{max} value in that subject, the subject's data without any adjustments can be included in all pharmacokinetic measurements and calculations (i.e. the predose value will not be changed to zero). If the predose value is greater than 5% of C_{max}, the subject should be dropped from all statistical evaluations. The individual pharmacokinetic parameters can be calculated and listed separately. Every effort will be made to include all concentration data in an analysis. If not possible, a case to case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

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

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

7.6 RANDOMISATION

Not Applicable, as only 1 dose group is planned

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 12 subjects in this trial. The planned sample size is not based on a power calculation. A group size between 8 and 12 per dose level is commonly used in

healthy subject trials and is considered sufficient for exploratory investigation of single/multiple dose safety and pharmacokinetics.

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

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) and other relevant regulations.

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

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects 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 subjects, and is stored in the ISF (Investigator Site File).

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 subject participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH / GCP and to

the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additionalsubject-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject'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

Case Report Forms (CRF) for individual subjects 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 CRF 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 subject, documented in their medical records, would be acceptable.
Before providing any copy of subjects' source documents to the sponsor the investigator must ensure that all subject identifiers (e.g. subject's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure subject confidentiality.

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

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

- Subject identification: gender, date or year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of Subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Subject's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a subject 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 subject or testing

conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject 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 CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and 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 subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject privacy will be ensured by using subject identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject'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 subject in the whole trial.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ("Last Patient Out").The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 PHARMACOKINETIC ANALYSES

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

[redacted]

$$t_{1/2,(ss)} = \frac{\ln 2}{\lambda_z}$$

[redacted]

[redacted]

AUC: The area under the curve will be calculated using the linear up/log down algorithm. If an analyte concentration is equal to or higher than the preceding concentration, the linear trapezoidal method will be used. If the analyte concentration is smaller than the preceding concentration, the logarithmic method will be used.

Linear trapezoidal rule ($t_2 > t_1$ and $C_{t2} \geq C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1\text{-}t2} = 0.5 \times (t_2 - t_1) \times (C_{t1} + C_{t2})$$

Logarithmic trapezoid rule ($t_2 > t_1$ and $C_{t2} < C_{t1}$):

The area of the trapezoid between the two data points (t_1, C_{t1}) and (t_2, C_{t2}) will be computed by:

$$AUC_{t1-t2} = \frac{(t_2 - t_1) \times (C_{t2} - C_{t1})}{\ln(C_{t2}/C_{t1})}$$

$AUC_{0\text{-}\infty}$: The area under the plasma concentration-time curve over the time interval from 0 extrapolated to infinity will be calculated according to the following equation

$$AUC_{0\text{-}\infty} = AUC_{0\text{-}tz} + \frac{C'_{tz}}{\lambda_z}$$

where C'_{tz} is the concentration predicted by the regression line for the time t_z (time of last measurable concentration of the analyte in plasma). The area under the concentration-time curve over the time interval from 0 to the last quantifiable plasma concentration ($AUC_{0\text{-}tz}$) will be calculated by the linear up/log down method as described above.

%AUC$_{tz-\infty}$: The percentage of the $AUC_{0-\infty}$ will be obtained by extrapolation according to the following equation:

$$\%\,AUC_{tz-\infty} = \frac{AUC_{0-\infty} - AUC_{0-tz}}{AUC_{0-\infty}} \times 100$$

[redacted]

$$MRT_{po} = \frac{AUMC_{0-\infty}}{AUC_{0-\infty}}$$

[redacted]

$$AUMC_{0-\infty} = AUMC_{0-tz} + \frac{C'_{tz} \times t_z}{\lambda_z} + \frac{C'_{tz}}{\lambda_z^2}$$

[redacted]

[redacted] = [redacted] / $AUC_{0-\infty}$

[redacted]

$$CL_{R,t1-t2} = \frac{Ae_{t1-t2}}{AUC[redacted]}$$

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

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

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

where

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

10.2 CLINICAL EVALUATION OF LIVER INJURY

10.2.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.6.1 (Protocol-Specified Significant Events), are to be further evaluated using the following procedures:

10.2.2 Procedures

Repeat the following lab tests: ALT, AST, ALP and bilirubin (total and direct) - within 24 to 48 hours. If ALT and/or AST ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN or an isolated elevation of AST and/or ALT ≥10-fold ULN (without an elevation of total bilirubin ≥2-fold ULN) are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.
In addition,

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

Clinical chemistry
alkaline phosphatase, albumin, prothrombin time (PT) or international normalised ratio, CK, CK-MB, ceruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, FPG, cholesterol, triglycerides
Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG, if anti-IgM and anti-IgG are not available, total anti HepD can be performed), Hepatitis E (Anti- HEV), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody

Hormones, tumor marker
TSH

Haematology

Thrombocytes, eosinophils, complete blood count (including differential)

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1
Date of CTP revision		17 Mar 2017
EudraCT number		Not applicable
BI Trial number		1321.6
BI Investigational Product(s)		Idarucizumab
Title of protocol		Open label Phase I trial in healthy Chinese male and female volunteers to investigate pharmacokinetics and pharmacodynamics of idarucizumab to reverse dabigatran anticoagulant activity
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		Flow Chart 1
Description of change		*Deleted* "X" sign of Blood sampling for PK of idarucizumab at day 1
Rationale for change		To keep the consistence between flow chart 1 and 2.
Section to be changed		Flow Chart 1
Description of change		*Deleted* The superscript 3 and 4 have been deleted for Laboratory / Urinalysis at day 11.
Rationale for change		To keep the consistence between flow chart 1 and 2.
Section to be changed		Flow Chart 2
Description of change		*Deleted* "X" sign of Physical examination at day 10(216 hours)

Rationale for change		To keep the consistence between flow chart 1 and 2.
Section to be changed		Section 3.3.4.1
Description of change		*Deleted* (except for serious adverse events (SAEs))
Rationale for change		Updates to reflect the updated AE reporting requirements
Section to be changed		Table 4.1.1:2
Description of change		3 days twice daily (b.i.d.) with a single dose on day 4 *Was change to* 3 days 220 mg twice daily (b.i.d.) with a single dose 220mg on day 4
Rationale for change		Provide more clear information about posology.
Section to be changed		Table 5.3.3:1
Description of change		*Deleted* Diff. Manual (if Diff. Automatic is abnormal)
Rationale for change		Diff Manual won't be conducted if Diff Automatic is abnormal
Section to be changed		Table 5.3.3:1
Description of change		*Deleted* Infectious Serology-and HIV-2
Rationale for change		Only HIV-1 antibody will be tested.
Section to be changed		Table 5.3.3:1
Description of change		*Deleted* Infectious Serology-RPR
Rationale for change		Only one type of method needs to be selected for syphilis test.
Section to be changed		Section 5.3.6.2
Description of change		*Added* The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
Rationale for change		To follow updated BI procedure, where data

		collection of screening failure subjects in phase I healthy volunteer studies.
Section to be changed		Section 7.3.5.1 and 7.3.5.2
Description of change		*Deleted* (001-MCS-36-472)
Rationale for change		BI's SOP won't be provided as reference.

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APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval–Clinical Monitor	[redacted]	17 Mar 2017 10:19 CET
Author-Trial Statistician		17 Mar 2017 10:56 CET
Approval-Therapeutic Area [redacted]		17 Mar 2017 11:16 CET
Approval-Team Member Medicine		17 Mar 2017 14:21 CET
Author-Trial Clinical Pharmacokineticist		21 Mar 2017 01:51 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed