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Extract from the Clinical Evaluation Report for idarucizumab

Proprietary Product Name: Praxbind

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TGA Health Safety Regulation

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- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of abbreviations

Abbreviation	Meaning
ACT	Activated clotting time
ADA	anti-drug antibodies (i.e. anti-idarucizumab and anti-dabigatran antibodies)
AE	adverse event
Aet1-t2	amount of analyte eliminated in urine from the time point t1 to t2
ALT	alanine transaminase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC0-inf	area under the concentration-time curve of the analyte in plasma/urine over the time interval from 0 extrapolated to infinity
AUCt1-t2	area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2
AUEC	Area under the effect curve
$AUEC_{above,2-12}$	mean area under the effect curve with consideration of baseline
BI 655075	idarucizumab
BI	Boehringer Ingleheim Pty Ltd
BID	twice-daily
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
C1.92,ss	2 h (C1.92,ss) plasma concentrations of sum dabigatran before the infusion of idarucizumab or placebo with those after restart of DE administration (C2,ss,12)
CK	creatinine kinase
CL	total clearance of the analyst in plasma / urine following extravascular administration

Abbreviation	Meaning
CL(/F)	total (apparent) clearance of the analyte in plasma following intervascular (extravascular) administration
CLR,t1-t2	renal clearance of the analyte from the time point t1 until the time point t2,
Cmax	maximum measured concentration of the analyte in plasma
Cpre,ss	comparison of trough plasma concentrations of sum dabigatran before the infusion of idarucizumab or placebo with those after restart of DE administration (Cpre,ss,12)
CrCL	creatinine clearance
CT	Computer tomography
CTR	Clinical trial report
DDI	drug-drug interaction
DE	dabigatran etexilate
dTT	diluted thrombin time
DVT	Deep vein thrombosis
ECG	electrocardiogram
ECT	ecarin clotting time
ELISA	enzyme-linked immunosorbent assay
Emax	maximum effect
ERmax,ss	maximum effect ratio at steady state
ETP	endogenous thrombin generation potential
F1.2	prothrombin fragment 1+2
Fab	the region on an antibody that binds antigen
fe	urinary excretion
FOCE	first-order conditional estimation (estimation method in NONMEM)
FPA	fibrinopeptide A
gCV	geometric coefficient of variation

Abbreviation	Meaning
GI	Gastrointestinal
gMean	geometric mean
HC	heavy chain
HPLC-MS/MS	high performance liquid chromatography coupled to tandem mass spectrometry
ICH	International Conference on Harmonisation
Ida	Idarucizumab
IFSD	idarucizumab-free sum dabigatran
IMP	importance sampling (estimation method in NONMEM)
ITS	iterative two-stage (estimation method in NONMEM)
IV	intravenous
LC	light chain
LLOQ	lower limit of quantitation
MCB	master cell bank
min	minute/s
MS/MS	tandem mass spectrometry
N	Number
NOMEM	non-linear mixed effects modelling program
PCC	prothrombin complex concentrate
PD	pharmacodynamics
PDCO	Paediatric Committee
PDS	PD analysis set
PE	Pulmonary embolism
PK	pharmacokinetics
PKS	PK analysis set
PopPK	population pharmacokinetics

Abbreviation	Meaning
PR	pulse rate
QT	time between the start of the Q-wave and the end of the T-wave in an ECG
QTc	QT corrected for heart rate
rFVIIa	recombinant factor VIIa
RIPA	radio-immunoprecipitation
RR	respiratory rate
SAE	serious adverse event
SAEM	stochastic approximation expectation maximization estimation method in NONMEM
SCE	Summary of clinical efficacy
SD	Standard deviation
SPR	surface plasmon resonance
ss	(at) steady state
T	infusion time
t1/2	terminal half-life of the analyte in plasma
t1/2,2	initial half-life
TIA	Transient ischaemic attack
Tmax	time from (last) dosing to the maximum measured concentration of the analyte in plasma
TNF-α	tumour necrosis factor-α
TS	treated set
TT	Thrombin time
tz	time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
V2	volume of the peripheral compartment
Vc	volume of the central compartment

Abbreviation	Meaning
Vd	Volume of distribution
Vd,ss	Volume of distribution in steady state
Vss	apparent volume of distribution at steady state following an intravascular administration
VTE	Venous thromboembolic events
Vz(/F)	apparent volume of distribution during the terminal phase λz following in intravascular (extravascular) administration
WCB	working cell bank

1. Introduction

This is a submission to register a new biological entity, idarucizumab as a specific reversal agent for dabigatran and is indicated in patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of the anticoagulant effects of dabigatran is required.

2. Clinical rationale

Pradaxa is an oral pro-drug of dabigatran, a direct-acting thrombin inhibitor that has been shown to be effective in the prevention or reduction of thrombotic events in: patients with non-valvular atrial fibrillation; patients with deep vein thrombosis or pulmonary embolism who have been treated with a parenteral anticoagulant for 5-10 days; patients who have previously received anticoagulant therapy for treatment of venous thromboembolism in orthopaedic surgery patients at risk for post-operative DVT.

Anticoagulation therapy is a mainstay of treatment and prevention of pathologic thrombosis in these different clinical settings. However, as with all anticoagulants, bleeding is a potential side effect especially during emergency surgery or other urgent invasive procedures with dabigatran . In RE-LY, in patients with atrial fibrillation, the annualised rate of emergency surgery was 1.5% and 1.7% for patients treated with DE 150 and DE 110, respectively. The major bleeding rates in patients treated with dabigatran etexilate 150 mg bid in RE-LY were approximately 3% per year (3 events per 100 patient-years), of which half (1.5%) were categorised as life-threatening and in rare cases (0.2%), the bleeding was fatal (Eikelboom, 2011).

To date, acute management of serious bleeding in patients on dabigatran etexilate, including life-threatening bleeds, is limited to supportive care, administration of blood or blood products and, in suitable patients, consideration of haemodialysis to remove the drug (Weitz, 2012; Majeed, 2013). Similarly, there are no other alternatives for the management of dabigatran-associated peri-operative bleeds. Until now, there has been no treatment that directly reverses the pharmacological effect of dabigatran. The ability to safely reverse the anticoagulant effect of dabigatran in patients who require rapid reversal could improve the surgical risk of patients requiring emergency surgery, improve the management of serious bleeding events and further increase the overall safety profile of anticoagulation therapy with dabigatran.

Idarucizumab directly, rapidly and specifically neutralises dabigatran's anticoagulant effect due to its very high affinity for dabigatran (Kd = 2.1pM). This affinity is approximately 300-fold higher than the affinity of dabigatran for thrombin (Kd = 0.7 nM). This high affinity for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab. In dynamic equilibrium, any thrombin-bound dabigatran (or other plasma protein-bound dabigatran) will equilibrate with unbound dabigatran and rapidly thereafter be bound by any free idarucizumab. Idarucizumab itself has no known pharmacologic effect and preclinical data have shown that it does not bind to factors in the coagulation cascade or other antithrombotics. The clinical development program consists of three completed studies in volunteers (studies 1321.1, 1321.2 and 1321.5) and one ongoing study in patients (1321.3). Each Phase I study in volunteers documented the safety of idarucizumab over a range of doses and also explored the dose-response for reversal of dabigatran anticoagulant effect. Clinical studies evaluated pharmacologic reversal of the anticoagulant effect of dabigatran.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained:

- Three clinical pharmacology studies which provided both pharmacokinetic and pharmacodynamic data. Three Phase 1 studies (1321.1, 1321.2 and 1321.5) in 283 healthy volunteers documented the safety of idarucizumab over a range of doses but also explored the dose-response for reversal of dabigatran anticoagulant effect.
- One population pharmacokinetic analyses (01-02-05).
- One pivotal Phase 3 efficacy/safety, uncontrolled, open-label, case-series study (1321.3) which is still ongoing; only interim report (cut off was 2 Dec 2014) from first 26 patients was provided in this submission (Module 5.3.4.2). This is the only study in patients evaluating efficacy of idarucizumab in emergency situations, when rapid and safe reversal of the anticoagulant effects of dabigatran is required.
- Pooled analyses of the three Phase 1 studies in healthy volunteers, integrated summary of efficacy and safety.

  Comments: A 4-month safety update summarises safety and efficacy data from this ongoing study and provides data in 123 patients (Module 5.3.5.3). However, the cover letter, clinical overview and clinical summary of efficacy in Modules 1 and 2 of the current dossier only summarise data in 26 patients from study 1321.3. The sponsors have been asked to provide clarification on why data from the 123 patients was not included in the summary of efficacy or overview especially considering fact that both FDA and EMA mention data from 123 patients in their approval statements and labelling.

3.2. Paediatric data

The submission did not include paediatric data. As Pradaxa (dabigatran etexilate) is used in adults only, there is no paediatric data for idarucizumab since the use of idarucizumab in the paediatric population is considered not relevant. A protocol to treat children who may be treated with dabigatran within a clinical trial is in development, in agreement with the PDCO in the European Union.

3.3. Good clinical practice

The trials were carried out in compliance with the clinical trial protocol (CTP), in accordance with the principles of the Declaration of Helsinki, in accordance with the ICH-GCP, and in accordance with applicable regulatory requirements and Boehringer Ingelheim (BI) standard operating procedures (SOPs).

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

Table 1 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	Safety, tolerability, and PKs	1321.1	PKs of IV doses of idarucizumab and to explore the effect of different doses of idarucizumab administered on the steady state PK/PD of dabigatran
		1321.2	PKs and PDs of idarucizumab and to establish the idarucizumab dose(s) effective in reversing dabigatran-induced prolongation of blood coagulation time.
PK in special populations	Healthy Japanese subjects	1321.5	PKs of idarucizumab and to explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran
Population PK analyses	Healthy subjects	01-02-05	Characterise the PopPK of idarucizumab and its binding interaction with dabigatran and to provide PK/PD simulations

* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Analytical method for the determination of idarucizumab

To support the idarucizumab clinical development program specific and sensitive ELISA, methods for the quantitation of total idarucizumab in human plasma and urine were developed and validated at Covance Laboratories, Inc., Chantilly, Virginia, USA. The LLOQ of the methods was 1 µg/mL in both plasma and urine.

4.2.2. Physicochemical characteristics of the active substance

Idarucizumab is a humanised monoclonal antibody fragment (Fab) molecule derived from murine IgG1 isotype antibody molecule. The idarucizumab 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 disulphide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. The predicted molecular mass of idarucizumab is 47,766 Da.

Idarucizumab drug substance is a colourless to slightly yellow, clear to slightly opalescent solution. The pH of the final formulated idarucizumab drug substance is 5.5. The melting point of the idarucizumab molecule is 84.4°C.

Each 50 mL vial of PRAXBIND/PRADTURN solution for injection/infusion contains 2.5 g of idarucizumab (50 mg/mL).

4.2.3. Pharmacokinetics in healthy subjects

4.2.3.1. Absorption

Sites and mechanisms of absorption

Idarucizumab is administered via IV injection or infusion. Following administration of 5 g (the proposed dose) of the commercial formulation of idarucizumab to 6 healthy subjects aged 45 to 64 years in Study 1321.2, the median Tmax (range) of idarucizumab occurred at 0.1 h (0.100 – 0.250) after dosing, the mean t1/2 (gCV%) was 10.3 h (18.9) and the mean Cmax (gCV%), AUC0-inf and clearance (CL) values for idarucizumab were 25 µM/L (16.9%), 37 µM.h/L (18.4%) and 47.1 mL/min (18.4%), respectively.

4.2.3.2. Bioavailability

Absolute bioavailability

Not applicable.

Bioavailability relative to an oral solution or micronised suspension

Not applicable.

Bioequivalence of clinical trial and market formulations

As described in the section on Formulation development of this report, the selected formulation for marketing was used in all the clinical studies. The only difference in presentation was that the fill volume was increased from 20 mL/vial to 50 mL/vial to provide the desired dose for clinical use. Batches with both fill volumes were only used in Study 1321.1.

Bioequivalence of different dosage forms and strengths

Not applicable.

Bioequivalence to relevant registered products

Not applicable.

Influence of food

Not applicable.

Dose proportionality

Part 1 of Study 1321.1 examined the dose proportionality of idarucizumab following single doses of 20 mg, 60 mg, 200 mg, 600 mg, 1.2 g, 2 g, 3 g, 4 g, 6 g and 8 g as a long infusion (1 h). The results indicated that following the 60 min infusion, geometric mean Cmax and AUC0-inf increased proportionally with dose from Cmax values of 79.9 nmol/L (gCV: 15.1%) to 33900 nmol/L (gCV: 13.2%) and from AUC0-inf values of 146 nmol.h/L (gCV: 19.8%) to 63800 nmol.h/L (gCV: 15.6%) after infusion of 20 mg to 8 g idarucizumab.

Bioavailability during multiple-dosing

No clinical studies have examined the PKs of idarucizumab following daily doses over multiple days.

Effect of administration timing

Not applicable.

4.2.3.3. Distribution

Volume of distribution

Following administration of a single IV dose of 4 g idarucizumab as a long- (60 min, Part 1) or as a short-infusion (5 min, Part 2) to healthy males in Study 1321.1, the mean volume of distribution (%gCV) was 6.96 L (17.8) and 8.25 L (26.3), respectively. A similar result was obtained from the PopPK analysis (Study PopPK 01-02-05), which indicated that following IV administration to healthy subjects, the idarucizumab plasma concentration-time data was best described by a linear three-compartment model that was not influenced by binding to dabigatran. On summing, the volumes for the three compartments a Vss of 9.22 litres was obtained.

Plasma protein binding

Plasma protein binding was determined by surface plasmon resonance (SPR). These studies indicated that neither idarucizumab alone nor the idarucizumab-dabigatran complex bind to albumin or to other plasma proteins.

In addition, idarucizumab was tested for its ability to bind to other substrates of thrombin, including factor V, factor XIII, protein C, von Willebrand factor, S-2238 (a specific substrate of thrombin), 10% pooled plasma (n=6 individuals), dabigatran, and peptides representing known thrombin cleavage sites in FV, FVIII, FXIII, protein C, fibrinogen and PAR1 using surface plasmon resonance (SPR). The studies showed there was no binding of idarucizumab to any of these thrombin substrates, except dabigatran.

Erythrocyte distribution

Not applicable.

Tissue distribution

The volume of distribution (see above) indicates that idarucizumab is unlikely to be distributed to the tissues.

4.2.3.4. Metabolism

Interconversion between enantiomers

Not applicable.

Sites of metabolism and mechanisms / enzyme systems involved

Not applicable.

Non-renal clearance

Not applicable.

Metabolites identified in humans

Not applicable.

Pharmacokinetics of metabolites

Not applicable.

Consequences of genetic polymorphism

Not applicable.

4.2.3.5. Excretion

Routes and mechanisms of excretion

Not applicable.

Mass balance studies

Not applicable.

Renal clearance

Not applicable.

Intra and inter individual variability of pharmacokinetics

The inter-subject coefficient of variation values for idarucizumab Cmax and AUC0-inf following a single 5 g dose in healthy subjects were 16.9% and 18.4%, respectively. The PopPK study provided estimates for the inter-subject variability on idarucizumab CL, Vc and V2 of 11.9%, 14.8% and 322%, whereas, the estimated proportional- and additive-residual errors were 0.176 and 0.062, respectively.

4.2.4. Pharmacokinetics in the target population

No studies provided an in depth examination of the PKs of idarucizumab in the target population. However, the on-going Phase 3 study, 1321.3, provided a limited PK analysis of data from 88 patients who had been administered a 5 g dose of idarucizumab. The patients were separated into two groups depending on indication: Group A included patients treated with dabigatran who had uncontrolled or life-threatening bleeding requiring urgent intervention, whereas, patients in Group B had been treated with dabigatran but now required emergency surgery or other invasive procedure. Results indicated that there were no apparent differences in the mean concentrations between the two groups. By 4 h, concentrations declined approximately 80% from a peak of ~25,000 nM/L. By 12 h concentrations had declined by almost 99% and remained so at 24 h.

The PK of idarucizumab in patients were similar to that seen in healthy Phase I volunteers; however, there was a larger variability and a slower decrease in plasma concentrations in patients than in healthy subjects. The sponsor suggests that this may be due to the decreased renal function in the patient population, since a major route of elimination of idarucizumab is the kidney, either via filtration or catabolism.

4.2.5. Pharmacokinetics in other special populations

4.2.5.1. Pharmacokinetics in subjects with impaired hepatic function

Idarucizumab has not been studied in patients with hepatic impairment.

4.2.5.2. Pharmacokinetics in subjects with impaired renal function

Study 1321.2 compared the PKs of idarucizumab in healthy subjects and in subjects with mild renal impairment following a single dose of 5 g and in subjects with moderate renal impairment following 2 short infusions of each 2.5 g 1 h apart. In subjects with mild renal impairment, gMean Cmax and AUC0-inf were increased approximately 1.28- and 1.44-fold, respectively compared to healthy subjects and for subjects with moderate renal impairment 2.04- and 1.84-fold, respectively compared to healthy subjects. Idarucizumab gMean CL was reduced from 47.1 mL/min in healthy subjects to 32.8 mL/min and 25.7 mL/min in subjects with mild and moderate renal impairment, respectively.

4.2.5.3. Pharmacokinetics according to age

In healthy elderly subjects aged 65 to 80 years, idarucizumab Cmax and AUC0-inf were increased 1.13- and 1.19-fold, respectively compared to healthy subjects aged 45 to 64 years following a single 5 g dose idarucizumab. Idarucizumab CL was reduced from 47.1 mL/min in healthy subjects aged 45 to 64 years to 39.6 mL/min in healthy subjects aged 65 to 80 years.

4.2.5.4. Pharmacokinetics related to genetic factors

Not examined.

4.2.5.5. Pharmacokinetics (in other special population / according to other population characteristic)

Japanese subjects

Study 1321.5 examined the idarucizumab PKs following a single 4 g IV infusion (over 5 min) to healthy Japanese males. The results indicated that the Cmax and AUC0-inf of idarucizumab in Japanese subjects were 28100 nmol/L and 37600 nmol.h/L, respectively. The corresponding values in White males were 15700 nmol/h and 31000 nmol.h/L, respectively, indicating that idarucizumab exposure was higher in Japanese subjects than in White subjects.

4.2.6. Pharmacokinetic interactions

4.2.6.1. Pharmacokinetic interactions demonstrated in human studies

Interaction between idarucizumab and dabigatran

As idarucizumab is a specific reversal agent for dabigatran, which is intended for use when rapid reversal of the anticoagulant effects of dabigatran is required, all three Phase I studies examined the PK interaction between the two drugs, as did the PopPK study.

Effect of dabigatran on idarucizumab PKs

Part 2 of Study 1321.1 examined the PKs of idarucizumab following a short IV infusion (5 min) of 1 g, 2 g and 4 g idarucizumab in the presence and absence of steady-state dabigatran (200 mg BID) in healthy White males. Although there were no obvious differences in the shape of the idarucizumab plasma concentration time profiles when idarucizumab was co-administered with dabigatran, the idarucizumab AUC0-inf was decreased by approximately 1.20-fold following a 1 g dose of idarucizumab in combination with steady-state dabigatran compared to when idarucizumab was administered alone. By contrast, following the 2 g idarucizumab dose, the AUC0-inf was similar in both the presence and absence of dabigatran, whereas, at the 4 g dose of idarucizumab, the AUC0-inf of idarucizumab was 1.20-fold higher in the presence of dabigatran. Changes in idarucizumab Cmax also followed a similar pattern to AUC0-inf.

In Study 1321.2, idarucizumab was only administered following attainment of steady-state levels (or close to steady-state levels) of dabigatran; therefore, the effect of dabigatran on the PKs of idarucizumab could not be determined.

Study 1321.5 examined the PKs of idarucizumab in the absence (Part 1) and presence of steady-state dabigatran (Part 2) in healthy Japanese males. In contrast to Study 1321.1, there was little difference in idarucizumab exposure when given alone or in the presence of dabigatran. For example, the difference in idarucizumab Cmax and AUC0-inf following a 4 g dose in the presence or absence of dabigatran were 1.07-fold and 1.09-fold, respectively. Urinary excretion (fe) and CLR with dabigatran were approximately 2 to 3 times higher than those without dabigatran for idarucizumab 1000 to 4000 mg, whereas they were comparable at highest dose of idarucizumab 8000 mg alone and 2500 mg + 2500 mg with dabigatran. The PopPK analysis (PopPK 01-02-05,), which included the data from all 3 Phase I studies, also indicated that idarucizumab disposition was not influenced by binding to dabigatran.

Overall, the results from the clinical trials and PopPK study provided indicate that idarucizumab PKs may be slightly affected by administration with steady-state dabigatran (up to 1.20-fold). However, any differences in idarucizumab exposure following administration with or in the absence of dabigatran are unlikely to be clinically significant.

Effect of idarucizumab on dabigatran PKs

Analytical methods for determining unconjugated and sum dabigatran in human plasma and urine: A number of highly specific HPLC-MS/MS methods were developed to identify unconjugated and sum dabigatran (i.e. dabigatran plus its pharmacologically active glucuronides) in human plasma and urine. For the detection of plasma levels the assays were

validated over the concentration range of 5.00 to 5000 ng/mL of dabigatran, whereas, for the determination of dabigatran in urine the methods were validated over the concentration range of 20.0 to 10000 ng/mL of dabigatran.

Analytical methods for determining unbound and unbound sum dabigatran in human plasma and urine: In order to determine the concentration of unbound dabigatran and unbound (sum) dabigatran (i.e. (sum) dabigatran that is neither bound to idarucizumab nor to plasma proteins), ultrafiltration was used to separate unbound dabigatran from protein bound analytes. The analyte levels were then determined in the resulting plasma ultrafiltrates using HPLC-MS/MS methods, which were validated over the concentration range of 1.00 to 400 ng/mL.

Study results

All three Phase I studies indicate that immediately following IV infusion with all 4 doses of idarucizumab examined (i.e. 1 g, 2 g, 4g and 5 g), unbound sum dabigatran plasma concentrations decreased to approximately or to below the lower limit of quantification (LLOQ) and that this decrease was idarucizumab dose-dependent. For instance, in Study 1321.1 the gMean AUC2-12,ss values for unbound sum dabigatran were 805 ng.h/mL on Day 3 (all subjects from Part 2 pooled, N=35), and 754, 161, 20.9, and 11.9 ng.h/mL for subjects on placebo (N=9), 1 g (N=9), 2 g (N=9) and 4 g (N=8) idarucizumab on Day 4, respectively. The dose-dependent decrease in unbound sum dabigatran was accompanied by an idarucizumab-dose-dependent increase in sum dabigatran. For instance, the gMean AUC2-12,ss values for sum dabigatran were 1090 ng.h/mL on Day 3, and 1060, 2330, 2340, and 2770 ng.h/mL for subjects on placebo, 1 g, 2 g and 4 g idarucizumab on Day 4, respectively.

In comparison with urinary excretion in the absence of idarucizumab, urinary excretion was transiently reduced in the presence of idarucizumab. For instance, the amount of sum dabigatran excreted over the dabigatran dosing interval Ae0-12,ss was 6600 µg on Day 3 (all subjects from Part 2 pooled, N=34), and 6870, 5160, 3820 and 3860 µg for subjects on placebo (N=9), 1 g (N=9), 2 g (N=9) and 4 g (N=8) idarucizumab on Day 4.

Re-exposure to dabigatran

In Study 1321.2, the healthy subjects, who had been administered 2.5 or 5 g of idarucizumab, had dabigatran treatment restarted 26 h after the 7th DE dose (corresponding to 24 h after the end of the idarucizumab infusion). This continued until Day 7 to investigate whether a normal dabigatran treatment with normal dabigatran anticoagulation effects could be re-established after administration of idarucizumab. A comparison of trough (Cpre,ss) and 2 h (C1.92,ss) plasma concentrations of sum dabigatran before the infusion of idarucizumab or placebo with those after restart of DE administration (Cpre,ss,12 and C2,ss,12) revealed no effect on exposure to sum dabigatran 24 h prior to infusion of idarucizumab.

No studies examined the drug-drug interaction between idarucizumab and other drugs.

4.2.6.2. Clinical implications of in vitro findings

In vitro studies indicate that the addition of a range of coagulation factors had no effect on the ability of idarucizumab to reverse the anti-coagulatory effects of dabigatran. These factors included: prothrombin complex concentrate (PCC), which is a preparation made from fresh frozen human blood that contains the II, VII, IX and X coagulation factors; activated prothrombin complex concentrate (aPCC), which contains inactive and active forms of the four coagulation factors listed above; and recombinant factor VIIa (rFVIIa), which is a glycoprotein produce by recombinant technology that has similar characteristics and functions to native blood factor VII. Further in vivo studies indicated that idarucizumab has no effect on the anticoagulant activity of other clinically used agents such as vitamin K antagonists, factor Xa inhibitors, heparins or other DTIs that are different in structure to dabigatran, such as hirudin and argatroban. By contrast, results from an in vivo bleeding model, suggested that idarucizumab only partially reversed

dabigatran induced elongation of bleeding time following administration of dabigatran in combination with platelet agents.

4.2.7. Population PK

The PopPK study (Study PopPK 01-02-05), which examined the impact of race, sex, age, renal clearance and weight on idarucizumab PKs, identified that idarucizumab disposition following IV administration was best described by a linear, three compartment model, which was not influenced by binding to dabigatran.

Analysis of the data from the three Phase 1 studies identified that idarucizumab CL was a function of renal clearance and for a typical subject (i.e. the population prediction median) idarucizumab CL was 2.3 L/h. Based on these findings idarucizumab clearance ranged from 1.59 L/h in subjects with renal impairment (CrCL=40 mL/min) to 2.62 L/h in healthy subjects (CrCL=120 mL/min). In addition, idarucizumab fractional central Vd was determined to be a function of body weight and relative to a subject with a typical body weight of 70 kg and a Vd of 3.3 L (i.e. the normalised population average Vd), Vd ranged from 2.57 L for an individual weighing 50 kg to 4.42 L for an individual weighing 120 kg. By contrast, sex, age and body weight were not significantly correlated with idarucizumab clearance after adding CrCL to the model, whereas clearance, was approximately 11% lower in Japanese subjects when compared to White subjects.

4.3. Evaluator's conclusions on pharmacokinetics

- Idarucizumab is a humanised monoclonal antibody fragment, which is administered via IV injection or infusion.

ADME

- Following administration of 5 mg (the proposed dose) of idarucizumab to healthy subjects aged 45 to 64 years the median Tmax (range) of idarucizumab occurred at 0.1 h (0.100-0.250) after dosing.
- Following a 60 min infusion of IV idarucizumab, geometric mean Cmax and AUC0-inf increased proportionally with dose from Cmax values of 79.9 nmol/L (gCV: 15.1%) to 33900 nmol/L (gCV: 13.2%) and from $AUC_{0\text{-}inf}$ values of 146 nmol.h/L (gCV: 19.8%) to 63800 nmol.h/L (gCV: 15.6%) after infusion of 20 mg to 8 g idarucizumab.
- Following administration of a single IV dose of 4 g idarucizumab as a long (60 min, Part 1) or as a short infusion (5 min, Part 2) to healthy males the mean volume of distribution (%gCV) was 6.96 L (17.8) and 8.25 L (26.3), respectively.
- Idarucizumab alone and the idarucizumab-dabigatran complex do not bind to albumin or to other plasma proteins.
- The volume of distribution indicates that idarucizumab is unlikely to be distributed to the tissues.
- The inter subject coefficient of variation values for idarucizumab Cmax and $AUC_{0\text{-}inf}$ following a single 5 g dose in healthy subjects were 16.9% and 18.4%, respectively.
- The estimated inter subject variability on idarucizumab CL, Vc and V2 were 11.9%, 14.8% and 322%, whereas, the estimated proportional and additive residual errors were 0.176 and 0.062, respectively.

4.3.1.1. Renal impairment

- In subjects with mild renal impairment Cmax and $AUC_{0\text{-}inf}$ were increased approximately 1.28 and 1.44 fold, respectively compared to healthy subjects and for subjects with moderate renal impairment 2.04 and 1.84 fold, respectively compared to healthy subjects.

- Idarucizumab CL was reduced from 47.1 mL/min in healthy subjects to 32.8 mL/min and 25.7 mL/min in subjects with mild and moderate renal impairment, respectively.

4.3.1.2. Effect of age

- In healthy elderly subjects aged 65 to 80 years, idarucizumab Cmax and $AUC_{0\text{-}inf}$ were increased 1.13 and 1.19 fold, respectively compared to healthy subjects aged 45 to 64 years following a single 5 g dose idarucizumab.
- Idarucizumab CL was reduced from 47.1 mL/min in healthy subjects aged 45 to 64 years to 39.6 mL/min in healthy subjects aged 65 to 80 years.

4.3.1.3. Japanese subjects

- In Japanese subjects following a 4 g IV infusion, the Cmax and $AUC_{0\text{-}inf}$ of idarucizumab were 28100 nmol/L and 37600 nmol.h/L, respectively. The corresponding values in white males were 15700 nmol/h and 31000 nmol.h/L, respectively indicating that idarucizumab exposure was higher in Japanese subjects than in White subjects.

4.3.1.4. Effect of dabigatran on idarucizumab PKs

- Overall, the results from the 3 Phase I clinical trials and PopPK study indicate that idarucizumab PKs may be slightly affected by administration with steady state dabigatran (up to 1.20 fold). However, any differences in idarucizumab exposure following administration with or in the absence of dabigatran are unlikely to be clinically significant.

4.3.1.5. Effect of idarucizumab on dabigatran PKs

- All three Phase I studies indicate that unbound sum dabigatran plasma concentrations decreased to approximately or to below the LLOQ immediately following IV infusion with all 4 doses of idarucizumab (that is, 1 g, 2g, 4 g and 8 g) and that this decrease was idarucizumab dose-dependent.
- The dose dependent decrease in unbound sum dabigatran was accompanied by a idarucizumab dose dependent increase in sum dabigatran.
- Urinary excretion of dabigatran was transiently reduced in the presence of idarucizumab compared to the urinary excretion in absence of idarucizumab.
- Re-exposure to dabigatran 24 h following idarucizumab administration resulted in dabigatran exposure similar to that seen prior to idarucizumab dosing.
- In vitro studies indicate that a range of blood coagulation factors had no effect on the ability of idarucizumab to reverse the effects of dabigatran. Idarucizumab had no effect on the anticoagulant activity of other clinically used agents.
- Results from an in vivo bleeding model indicated that idarucizumab only partially reversed the effects of dabigatran when dabigatran was co-administered with platelet agents.

4.3.1.6. PopPK analysis

- Idarucizumab disposition after IV administration was best described with a linear, three compartment model and was not influenced by binding to dabigatran.
- PopPK analysis indicated that idarucizumab CL was a function of renal clearance and provided a population median idarucizumab CL of 2.3 L/h. Results indicated that idarucizumab clearance ranged from 1.59 L/h in subjects with renal impairment (CrCL = 40 mL/min) to 2.62 L/h in healthy subjects (CrCL = 120 mL/min).
- In addition, idarucizumab fractional central Vd (3.3 L) was a function of body weight and increased from 0.78 for a 50 kg individual to 1.34 for a 120 kg individual. By contrast, sex, age and body weight were not significantly correlated with idarucizumab clearance after

adding CrCL to the model, whereas clearance, was approximately 11% lower in Japanese subjects when compared to non-Japanese subjects.

4.3.1.7. Limitations of PK studies

- Limited PK studies were undertaken in the target population.
- No clinical studies examined the interaction of idarucizumab with drugs other than dabigatran.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Note: All of the studies that provide PD findings also contain PK data and therefore have been previously summarised in this report.

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

5.2.1. Mechanism of action

Idarucizumab acts by selectively and potently binding to dabigatran and thereby reversing dabigatran-induced prolongation of blood clotting times.

5.2.1.1. Methods used to identify the primary PD effects of idarucizumab

Dabigatran is an oral anticoagulant used for the prevention of strokes and emboli after major orthopaedic surgery and to prevent strokes and other systemic emboli in people with non-valvular atrial fibrillation. It acts by specifically and reversibly inhibiting thrombin activity and generation, a key enzyme in the coagulation cascade that enables the conversion of fibrinogen to fibrin and ultimately the formation of thrombi. Thrombin inhibition results in the prolongation of coagulation markers such as diluted thrombin time (dTT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and thrombin time (TT) as well as activated clotting time (ACT) and it reduces endogenous thrombin generation potential (ETP). Therefore, the primary PD effects of idarucizumab were measured by assessing its ability to reverse the effects of dabigatran on these coagulation factors and ETP.

5.2.1.2. dTT assay

One assay that appears to be particularly well suited for gauging the anti-coagulation effects of dabigatran is the dTT assay as a recent article,[1] indicates that the dTT assay provides a linear response to dabigatran exposure over the dose range of 40 to 500 ng/mL and as such is superior to both the aPTT and TT assays for this purpose.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Idarucizumab alone

Study 1321.1 examined the effects of two doses of idarucizumab (8 g administered over 1 h and 4 g over 5 minutes) when given alone (i.e. in the absence of dabigatran) on the coagulation

[1] Avecilla ST, et al. Plasma-diluted thrombin time to measure dabigatran concentrations during dabigatran etexilate therapy. *Am J Clin Pathol.* 137: 572-4 (2012).

markers and ETP in healthy male subjects. The results indicated that idarucizumab had no apparent effect on the coagulation parameter dTT, ECT, aPTT, and TT when determined 15 min after end of the infusion, nor did it affect ETP. Similarly, in healthy Japanese males (Study 1321.5), coagulation parameter values for dTT, ECT, TT, aPTT, and ACT were unchanged following administration of idarucizumab. In addition, administration of idarucizumab alone had no effect on values of ETP, D-Dimer or prothrombin fragment 1+2 (F1.2).

Taken together, the results indicate that when idarucizumab was administered in the absence of dabigatran it had no effect on coagulation parameters nor did it have a prothrombotic effect.

Idarucizumab and dabigatran

In all three Phase I studies dabigatran (220 mg BID) consistently prolonged the clotting times of all clotting parameters examined (Figures 1-3). In Study 1321.1, unlike placebo, administration of 1 g idarucizumab to healthy males resulted in an immediate and complete reversal with subsequent partial return of the dabigatran anticoagulant effect (starting between 30 min to 2 h after the end of the infusion. Two (2) g idarucizumab resulted in immediate, complete, and sustained (over the entire observation period) reversal of dabigatran-induced prolongation of clotting times demonstrated by the clotting assays dTT and aPTT, while the mean ECT values between 6 and 16 h after end of the idarucizumab infusion were slightly above the ULN. Four (4) g idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT and aPTT. In addition, idarucizumab infusion also resulted in the reversal of the effects of dabigatran on the ETP and the shed blood parameter fibrinopeptide A (FPA).

Figure 1. Study 1321.1: mean effect time profiles (+/- SD) of dTT at dabigatran steady state after infusion of 1, 2 or 4 g idarucizumab or placebo 5 min on Day 4.

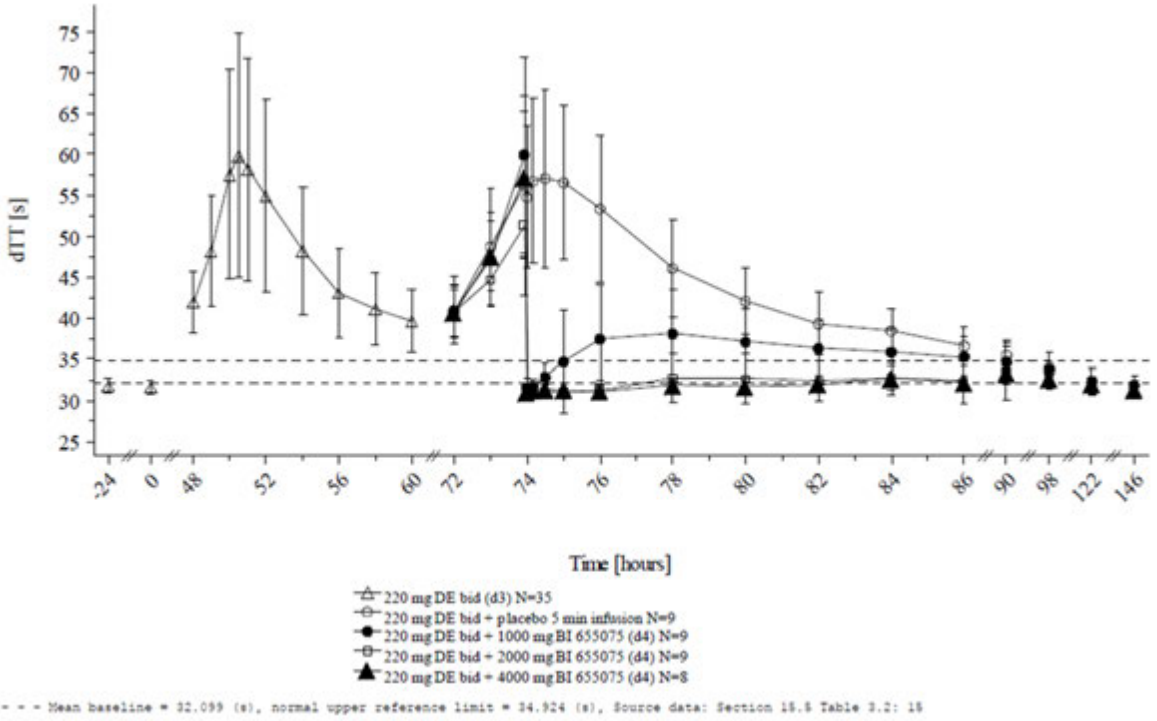


Figure 2. Study 1321.1: mean effect time profiles (+/- SD) of ECT at dabigatran steady state after infusion of 1, 2 or 4 g idarucizumab or placebo 5 min on Day 4.

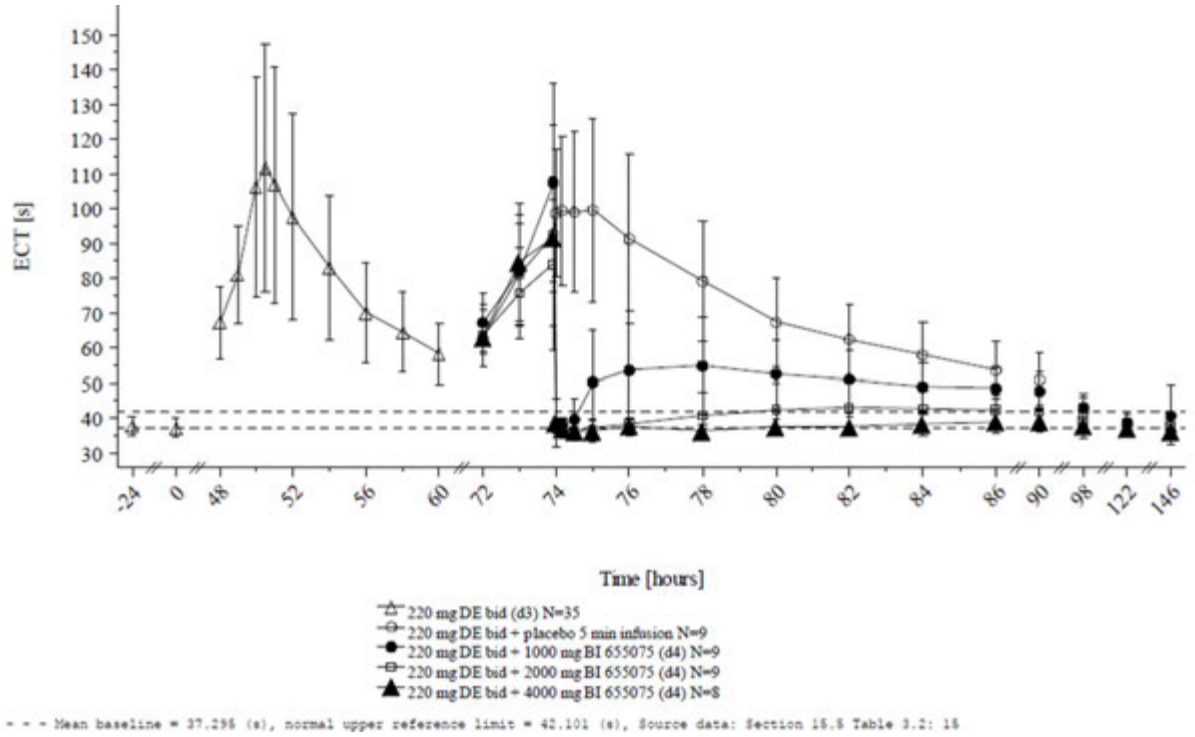
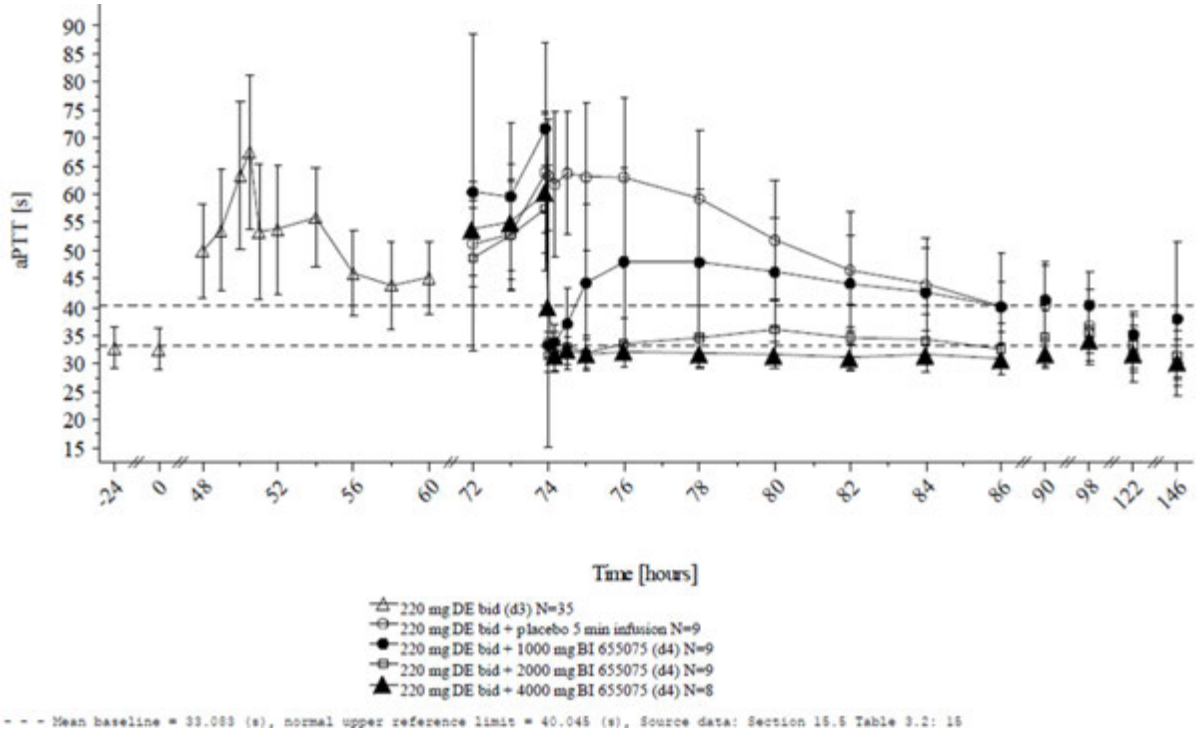


Figure 3. Study 1321.1: mean effect time profiles (+/- SD) of aPTT at dabigatran steady state after infusion of 1, 2 or 4 g idarucizumab or placebo 5 min on Day 4.



Similar results were identified in Studies 1321.2 and 1321.5. In Study 1321.2, treatment with both 2.5 g and 5 g idarucizumab in healthy subjects aged 45 to 64 years, once again unlike placebo, resulted in a reversal of dabigatran-induced elongation of dTT and ECT to the ULN within 10 min following the completion of the idarucizumab infusion. In Study 1321.5, all

coagulation parameters demonstrated an immediate and complete reversal below ULN in all groups after administration of idarucizumab 1000 mg to 2500 mg+2500 mg.

5.2.2.2. Secondary pharmacodynamic effects

Anti-idarucizumab antibodies

As part of the Safety Analyses, all three Phase 1 studies examined the subjects' plasma for the existence of "pre-existing" anti-idarucizumab antibodies (i.e. prior to administration of idarucizumab) and for the production of "treatment-emergent" anti-idarucizumab antibodies. Across the 3 studies, 40 of the 283 subjects (11 of 59 subjects randomised to placebo and 29 of 224 who received active drug) were identified as possessing pre-existing antibodies with cross-reactivity to idarucizumab.

Treatment-emergent anti-idarucizumab antibodies

In Study 1321.1, the formation of persistent treatment-emergent, anti-idarucizumab antibodies occurred in 1 of 118 subjects (i.e. the number of subjects on active treatment). This subject was identified as having no pre-existing idarucizumab antibodies at baseline and had persistently positive antibody titre post-treatment at 4 weeks and 3 months. A further six idarucizumab-treated subjects had transient, treatment-emergent anti-idarucizumab antibody responses, with positive titres at only 1 visit post-treatment.

In Study 1321.2, the formation of treatment-emergent, anti-idarucizumab antibodies was identified in 5 of 46 subjects who had no positive titre at baseline. Of these, one subject had a transient, treatment-emergent anti-idarucizumab antibody response, with a positive titre at only 1 visit post-treatment. Three subjects had responses that were characterised as possibly persistent, with positive titres only at the last sampling point (3-months follow-up). One subject had a persistent response with positive titres at the last two sampling time points.

In Study 1321.5, the formation of treatment-emergent anti-idarucizumab antibodies were identified in 4 of 60 subjects administered idarucizumab who had no pre-existing titres at pre-dose. Two subjects had a transient treatment-emergent anti-idarucizumab antibody response, without a positive titre at the last sampling point (3-month follow-up) and 2 subjects had responses classified as possibly persistent because anti-idarucizumab antibodies were still detected at the last sampling point.

Epitope specificity

Idarucizumab antibodies, both pre-existing and treatment-emergent, were primarily directed against the C-terminus of idarucizumab; however, there were instances where antibodies were directed against the variable regions of idarucizumab, antibodies that had initial specificity towards a C-terminus epitope but switched to a mixed specificity (C-terminus, constant region and/or variable region) and antibodies with specificity initially towards a C-terminus epitope but switched to a primarily anti-variable region specificity.

Effect of pre-existing anti-idarucizumab antibodies on PK and PD of idarucizumab

Plasma concentration time profiles of subjects with pre-existing anti-idarucizumab antibodies were within the variability of plasma concentration time profiles observed within their respective dose groups. Geometric mean dose-normalised AUC0-inf and dose-normalised Cmax of idarucizumab were similar in the presence or absence of pre-existing anti-idarucizumab antibodies. In Study 1321.1, the presence of pre-existing anti-idarucizumab antibodies did not appear to impact reversal of dabigatran-induced prolongation of clotting time for the parameters dTT and ECT.

5.2.3. Time course of pharmacodynamic effects

All three Phase 1 studies indicated that the duration of the reversal of dabigatran-induced elongation of clotting times was dependent on idarucizumab dose with a higher dose of idarucizumab correlating with a longer duration of reversal (Figures 1-3).

5.2.3.1. Re-exposure to idarucizumab

Study 1321.2 also examined the effect on duration of clotting time reversal of re-exposure to 2.5 mg idarucizumab two months following the initial exposure to 2.5 mg idarucizumab in 6 healthy subjects. Under these conditions, the effect on reversal of dTT was shorter following re-exposure compared to the initial exposure (up to 4h compared to at least 24 h, respectively), whereas, the duration of reversal of ECT was at least 24 h following both the initial exposure and re-exposure.

> *Comment: As repeat-dose exposure was only undertaken in 6 healthy subjects and these subjects were only administered half of the dose strength proposed for registration, it is difficult to suggest that these results provide an adequate demonstration of safety and efficacy of idarucizumab with repeat dosing. In addition, little to no information is provided regarding idarucizumab antibody formation following re-exposure.*

5.2.3.2. Re-dosing of DE

In Study 1321.2, pre-treatment with dabigatran and restart of dabigatran treatment 24 h after infusion of placebo or idarucizumab to healthy subjects aged 45 to 64 years resulted in similar trough and 2 h post-dose values of dTT, ECT, aPTT, and TT ratio to baseline.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

The results of Study 1321.1 identified that idarucizumab-induced reversal of dabigatran anticoagulation was dose-dependent in healthy males. This was demonstrated by the reduction with increasing dose of the ratio between the AUECabove,2-12 on Days 4 and 3 for dTT, ECT, aPTT and TT (Table 2). For instance although placebo had no effect on dabigatran-induced dTT elongation (AUECabove,2-12 ratio = 1.01), the corresponding ratios following administration of 1 g, 2g or 4 g idarucizumab were 0.26, 0.06 and 0.02, respectively.

Table 2. Study 1321.1.

	$AUEC_{above,2\text{-}12}$ [h] ratio Day 4/Day 3			
Dose group	dTT	ECT	aPTT	TT
Part 2 *(5 min infusion)*				
DE+plc	1.01	1.04	1.28	1.08
DE+1 g Ida	0.26	0.28	0.46	0.32
DE+2 g Ida	0.06	0.07	0.14	0.06
DE+4 g Ida	0.02	0.03	0.07	0.00
Part 3 *(5 min infusion)*				
DE+2 doses plc	1.02	1.22	1.68	1.11
DE+5 g+2.5 g Ida	0.01	0.02	0.03	0.00

Plc=placebo, Ida=idarucizumab

Similarly, Study 1321.5 identified a close linear relationship between unbound sum dabigatran plasma concentration and aPTT, dTT, TT and ECT in healthy Japanese males. Diluted TT correlated most closely with unbound sum dabigatran.

5.2.5. Genetic, gender and age related differences in pharmacodynamic response

Study 1321.2 indicated that there seemed to be no influence of sex, age, or renal impairment on the proportion of subjects attaining reversal of dabigatran-induced coagulation based on the investigated assays.

In addition, simulation results, undertaken as part of the PopPK analysis (Study 01-02-05), indicated that CrCL had no effect on the ability of idarucizumab to reverse dabigatran-induced elongation of ECT or dTT.

5.2.6. Pharmacodynamic interactions

No studies examined the PD interactions between idarucizumab and drugs other than dabigatran. However, due to the nature of the monoclonal idarucizumab antibody (i.e. it has high specificity for dabigatran, it lacks Fc-receptor mediated effects, it is neither a cytokine nor a cytokine modulator and no potential endogenous target for idarucizumab has been identified) the Sponsor argues direct interactions between idarucizumab and other drugs are highly unlikely.

> *Comment: Although the sponsor considers DDIs are unlikely, a complete absence of clinical DDI studies does little to support their contention. Therefore, it could be argued that DDI studies should be undertaken to examine whether interactions exist between idarucizumab alone or the idarucizumab-dabigatran complex and at least a small number of drugs that are typically co-administered in the target population.*

5.3. Evaluator's overall conclusions on pharmacodynamics

- Idarucizumab acts by selectively and potently binding to dabigatran and thereby reversing dabigatran induced prolongation of blood clotting times.
- In the absence of dabigatran, idarucizumab administration had no effect on coagulation parameters nor did it have a prothrombotic effect.
- Dabigatran consistently prolonged the clotting times of all clotting parameters. In healthy subjects, all doses of idarucizumab tested (1 g to 5 g) resulted in an immediate and complete reversal of dabigatran induced anticoagulant effects. In addition, the duration of the reversal of dabigatran induced elongation of clotting times was dependent on idarucizumab dose with a higher dose of idarucizumab correlating with a longer duration of reversal.
- The duration of the reversal of dabigatran induced dTT elongation was shorter following re-exposure to 2.5 g idarucizumab (2 months following the initial exposure) compared to the initial exposure (up to 4h compared to at least 24 h, respectively), whereas, the duration of reversal of ECT was at least 24 h following both the initial exposure and re-exposure.
- Pre-treatment with dabigatran and restart of dabigatran treatment 24 h after infusion of placebo or idarucizumab to healthy subjects resulted in similar trough and 2 h post dose values of dTT, ECT, aPTT, and TT ratio to baseline.
- Idarucizumab induced reversal of dabigatran anticoagulation was dose dependent in healthy males. For instance, although placebo had no effect on dabigatran induced dTT elongation ($AUEC_{above,2\text{-}12}$ ratio = 1.01), the corresponding ratios following administration of 1 g, 2g or 4 g idarucizumab were 0.26, 0.06 and 0.02, respectively.
- A close linear relationship between unbound sum dabigatran plasma concentration and aPTT, dTT, TT and ECT in healthy Japanese males was identified.
- There appeared to be no influence of sex, age, or renal impairment on the proportion of subjects attaining reversal of dabigatran induced coagulation based on the investigated assays.
- Simulation results, undertaken as part of the PopPK analysis, indicated that CrCL had no effect on the ability of idarucizumab to reverse dabigatran induced elongation of ECT or dTT.

5.3.1. Limitations of PD studies

- No studies examined the secondary PD effects of idarucizumab.
- Repeat dose exposure was only undertaken in 6 healthy subjects and these subjects were only administered half of the dose strength proposed for registration, therefore it is difficult to suggest that these results provide an adequate demonstration of safety and efficacy of idarucizumab with repeat dosing.
- Little to no information is provided regarding idarucizumab antibody formation following re-exposure.
- No studies examined the PD interactions between idarucizumab and drugs other than dabigatran.

6. Dosage selection for the pivotal studies

Study 1321.1 was a Phase I, randomised, double blind, placebo controlled Phase I study in 157 healthy male volunteers to investigate safety, tolerability and pharmacokinetics of single rising doses (20 mg to 8 g) of idarucizumab (Part 1) and to explore different doses of idarucizumab to reverse dabigatran anticoagulant activity in subjects pre-treated with dabigatran etixilate (Parts 2 and 3). The study design, endpoints, randomisation, blinding and details of the PK and PD results are provided.

In the absence of dabigatran, idarucizumab had no apparent effect on clotting parameters. In Parts 2 and 3, following administration of dabigatran 220 mg BID on Day 1 to Day 3 and 220mg OD on Day 4, median 2 h post dose sum dabigatran concentrations were comparable with the median exposure previously observed in patients with atrial fibrillation after 150 mg dabigatran etexilate (DE) twice daily dosing. Idarucizumab infusion resulted in reduction of unbound sum dabigatran concentrations to or below the LLOQ. The effect of idarucizumab on unbound sum dabigatran concentrations was dose-dependent over doses evaluated in this study (1g, 2g and 4g). When an at least equimolar dose of idarucizumab (≥2 g) was administered, gMean unbound sum dabigatran concentrations remained below 10 ng/mL over the entire observation period of 72 h.

In line with the reduction in concentration of unbound sum dabigatran, administration of ≥2 g idarucizumab resulted in immediate,[2] complete,[3] and sustained[4] reversal of dabigatran anticoagulation based on dTT and aPTT. Specifically, administration of:

- 1 g idarucizumab resulted in immediate and complete reversal with subsequent partial return of the dabigatran anticoagulant effect starting between 30 min to 2 h after the end of the infusion as determined by dTT, ECT, aPTT and TT;
- 2 g idarucizumab (that is, the dose calculated to be approximately equimolar to total dabigatran body load) resulted in immediate, complete, and sustained reversal with the clotting assays dTT and aPTT, while the mean ECT and TT values were slightly above the ULN from 6 to 16 h and 2 to 24 h after end of the idarucizumab infusion, respectively.

[2] Timing of the reversal: Reversal of dabigatran induced anti-coagulation occurred directly at theend of idarucizumab infusion.
[3] Magnitude of the reversal: Return of the mean coagulation time of a specific dose group to below the respective ULN.
[4] Durability of the reversal: mean coagulation times of the respective assay remain below ULN during the entire respective observation period. The term 'sustained for x h' was used if effect was less persistent.

- 4 g idarucizumab resulted in immediate, complete and sustained reversal with dTT, ECT and aPTT; TT values were slightly above the ULN from 12 to 24 h after end of the idarucizumab infusion
- 5 g + 2.5 g idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT, aPTT, and TT.

The main objective of the Phase Ib, randomised, double blind, placebo controlled, two way, crossover Study 1321.2 was to investigate safety, tolerability, PKs, and PDs of idarucizumab (1g, 2.5g and 5g single dose infusion) and to establish the idarucizumab dose(s) effective to reverse the dabigatran induced prolongation of the blood coagulation time in populations resembling the target patient population with respect to age and renal function.

After the end of infusion of all idarucizumab doses and in all populations unbound sum dabigatran plasma concentrations dropped to or below the LLOQ of 1 ng/mL concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The duration of the effect of idarucizumab on unbound sum dabigatran concentrations increased with dose. When higher idarucizumab doses (2.5 g or 5 g) were infused, gMean concentrations of unbound sum dabigatran remained below 11 ng/mL for the entire observation periods.

Complete reversal of individual dabigatran induced clotting time prolongation within 10 min after end of idarucizumab infusion was observed for all subjects of all dose groups for the clotting parameters dTT and ECT (primary analysis), as well as for aPTT and TT. Placebo infusion had no effect on the clotting parameters. Duration of reversal after idarucizumab infusion was dependent on the idarucizumab dose. Infusion of a total dose of 5 g idarucizumab resulted in sustained reversal of dabigatran induced clotting time prolongation over the entire observation period in healthy subjects (45-64 years) and healthy elderly (65-80 years) as well as subjects with mild renal impairment. When administered to subjects with moderate renal impairment, the total dose of 5 g was split into 2 times 2.5 g idarucizumab administered 1 h apart. Immediate, complete and sustained (in between infusions) reversal was observed after the first infusion of 2.5 g.

> *Comments: PD results from study 1321.2 confirm that 5 g idarucizumab is an efficacious dose that reverses dabigatran's anticoagulant activity at exposures in healthy subjects, elderly and subjects with mild or moderate renal impairment matching median exposures observed in patients with atrial fibrillation after 150 mg dabigatran etexilate twice daily dosing.*

In the Phase I, randomised, double blind within dose groups, placebo controlled, single centre Study 1321.5, single doses of idarucizumab and multiple doses of dabigatran etexilate (Part 2,only) were administered to Japanese young healthy male volunteers. Part 1 (n = 32) and Part 2 (n = 48) had a single rising dose design. The following doses of idarucizumab were administered: Part 1: 1, 2 and 4 g administered as 5 min infusion and 8 g administered as 1 h infusion; Part 2: 1, 2 and 4 g; as well as 2.5 g followed by 2.5 g 15 min later; all administered as 5 min infusion at steady state of a 220 mg dabigatran etexilate bid dosing regimen.

During idarucizumab infusion, a rapid and substantial decline of unbound sum dabigatran concentrations to at least the LLOQ (1 ng/mL) was observed. The duration of the effect of idarucizumab on unbound sum dabigatran concentrations increased with dose, whereby gMean concentrations of unbound sum dabigatran remained below 15 ng/mL after infusion of 2 g idarucizumab and below 4 ng/mL after infusion of higher idarucizumab doses.

In Part 2 of this study, dabigatran etexilate administration consistently prolonged clotting times of all clotting parameters in the absence of idarucizumab. Administration of:

- 1 g idarucizumab resulted in immediate and complete reversal as determined by dTT, ECT, aPTT and TT. By 1 h after end of infusion, all clotting parameters showed a partial return of the dabigatran anticoagulant effect.

- 2 g idarucizumab resulted in immediate and complete reversal as determined by dTT, ECT, aPTT and TT. By 2 h after end of infusion, all clotting parameters showed a partial return of the dabigatran anticoagulant effect.
- 4 g and 2.5 + 2.5 g idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT and aPTT. For TT, a partial return of dabigatran anticoagulation was observed between 24 to 48 h (4 g idarucizumab) and at 48 h (2.5 + 2.5 g idarucizumab) after infusion.

The selection of the clinical dose for patients and the demonstration of dose-response was based on biomarker response to different doses of idarucizumab and the concomitant reduction of the unbound sum dabigatran. PK/PD modelling was used to further substantiate dosing considerations. Clinical outcome data were not used in the estimation of the dosing. The calculation of the required dose of idarucizumab is based on a 1:1 stoichiometry of the binding of idarucizumab to dabigatran and the calculated total body load of dabigatran, reflected by the plasma concentrations and estimated volume of distribution. The target clinical dose of 5 g idarucizumab was selected based on the most extreme dabigatran concentrations seen in the RE-LY subgroup with high concentrations, e.g. 99th percentile of concentrations observed in subjects with moderate renal dysfunction based on a population pharmacokinetic model of data from this study and the range of observed trough concentrations ($C_{pre,ss}$) from that study (U09-3249-02). The 99th percentiles of trough and peak concentrations in patients with moderate renal failure were 543 and 861 ng/mL, respectively. These patients will have the highest dabigatran body loads. This coverage with 5 g idarucizumab is regarded as an overwhelming dose. Lower and higher idarucizumab doses have been tested in the Phase I studies.

> *Comments: Immediate and complete reversal was observed on the basis of the unbound fraction of sum dabigatran and coagulation parameters of dTT, ECT, TT and aPTT after administration of idarucizumab at steady state of dabigatran in all dose groups. The reversal effect was sustained at 4 g and the proposed therapeutic dose of 5 g. Overall, the proposed dose of 5 g (2 x 2.5 g) idarucizumab is appropriate and is being tested in the ongoing Phase III Study 1321.3 in the target patient population.*

7. Clinical efficacy

Indication 1:

> *PRAXBIND / PRADTURN is a specific reversal agent for dabigatran and is indicated in patients treated with PRADAXA (dabigatran etexilate) when rapid reversal of the anticoagulant effects of dabigatran is required:*
>
> – *for emergency surgery/urgent procedures; in life-threatening or uncontrolled bleeding.*

The assessment of efficacy of idarucizumab is primarily based on the reversal of dabigatran-induced anticoagulation as measured by biomarker tests in three studies in volunteers. In addition, the level of unbound sum dabigatran serves as a direct measure for the effectiveness of idarucizumab binding to dabigatran. The Phase I studies provide proof of concept as well as dose finding and therefore, at the same time, serve the purpose of a Phase II study. From an ongoing Phase III study, data from 26 patients with at least one month of follow up information by Dec. 2, 2014 is included in this SCE. The study evaluates the reversal effects of idarucizumab in the target population, based on coagulation tests, and allows for some insights into the clinical outcomes. Efficacy assessment will not be based on clinical outcomes due to the complex and heterogeneous emergency situations in the target population and the lack of a control group. However, outcomes are collected as secondary endpoints according to the trial protocol.

> *Comments: Due to the different nature of this submission, there were no real 'pivotal efficacy' studies as only interim data from the only Phase 3 study was provided. The interim*

results from the only Phase 3 study will be discussed in section 7.1.1. The main evidence is from the three Phase 1 studies in healthy volunteers; these were evaluated and discussed in detail in Sections 4, 5 and 6 above. A comparison and analysis of results across Phase 1 studies will be covered.

7.1. Study 1321.3

7.1.1. Study design, objectives, locations and dates

This was a Phase 3, open-label, uncontrolled, case series, multicentre study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab (BI 655075) in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures. RE-VERSE AD trial (A study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran). It is planned to treat approximately 200 to 300 patients with a total dose of 5 g (two 2.5g vials) of idarucizumab.

The primary objective is to demonstrate reversal of the anticoagulant effect of dabigatran. The secondary objectives are the assessment of bleeding, clinical outcomes, safety and the pharmacokinetics of dabigatran in the presence of idarucizumab. The study was initiated on 01 June 2014 with the interim cut-off date of 02 Dec 2014. Up to the cut-off date of 24 Oct 2014, 26 patients were included in Europe (Belgium, Finland, Poland, Spain), North America (Canada, USA), Asia (Hong Kong), and New Zealand. However, the 4 Month Safety Update includes clinical data from 123 patients recruited into RE-VERSE AD up to April 1, 2015, including the 26 patients reported in the earlier interim analysis (provided in Module 5.3.4.2). The last recruited patient was followed for 1 month, with an additional 7 days to account for patient scheduling and resolving important data queries. A data snapshot was taken on May 7, 2015. Central laboratory assessments (clotting tests and pharmacokinetics of dabigatran and idarucizumab) required greater lead times and analyses of these data were available for 90 of the 123 patients reported in this safety update.

Comments: Since the 4-month safety update provided in Module 5.4.3) includes the 26 patients reported in the earlier interim analysis, the efficacy results provided in the 4-month safety update will be evaluated and discussed below in sections 7.1.1.7 to 7.1.1.13.

7.1.2. Inclusion and exclusion criteria

The main inclusion criteria were: Age > 18 years, written informed consent and all patients were confirmed as being treated with dabigatran. The determination of whether the patient was being treated with DE was based on information provided by the patient, or by a patient representative (family member/relative), or the patient's physician. Baseline (pre-dose) blood samples for PK/PD measurements were to be taken in all patients.

Group A included dabigatran-treated patients seen in the Emergency Department (ED) of a hospital who exhibit signs and symptoms of (overt) uncontrolled bleeding requiring urgent medical or surgical intervention. Group B included dabigatran treated patients seen in the Emergency Department of a hospital who require emergency surgery or other medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure.

The main exclusion criteria were:

- Group A: Patients with minor bleeding (e.g. epistaxis, hematuria) who could have been managed with standard supportive care; patients with no clinical signs of bleeding; contraindications to study medication that included known hypersensitivity to the drug or its excipients (subjects with hereditary fructose intolerance may have reacted to sorbitol).
- Group B: A surgery or procedure which was elective or where the risk of uncontrolled or unmanageable bleeding was low; contraindications to study medication that included

known hypersensitivity to the drug or its excipients (subjects with hereditary fructose intolerance may have reacted to sorbitol).

7.1.3. Study treatments

The total dose is 5 g (two 2.5g vials) given by intravenous infusion. A single vial contains 2.5g of Idarucizumab. Patients receive a 2.5 g vial of study medication and a second 2.5 g vial within the next 15 minutes. There was no comparator treatment. No dosing or patient management decisions were based on central lab determination of reversal.

7.1.4. Efficacy variables and outcomes

Biomarker endpoints were the basis for determination of efficacy in this trial. Ecarin clotting time (ECT), diluted Thrombin Time (dTT), activated Partial Thromboplastin Time (aPTT) and Thrombin Time (TT) were measured in a central laboratory. Serial plasma samples were taken before and up to 24 hours after idarucizumab administration for the determination of dabigatran and idarucizumab PK, as well as for coagulation time measurements, including dTT, ECT, aPTT and TT. There was also local assessment of aPTT.

> *Comments: The coagulation tests used for the primary endpoint are standard tests used in the evaluation of a medication with this mechanism of action. However, it is important to note that some biomarkers may have been only for investigational use, for example, the dTT assay was investigational in the USA.*

The primary study endpoint is the maximum reversal[5] of anticoagulant effect of dabigatran based on central laboratory determination of dTT or ECT, at any time point from the end of the first infusion up to 4 hours after the completion of the last infusion. Reversal of anticoagulant effect was characterised by the maximum reversal achieved for each patient. The proportion of patients that achieved at least 100%, 80%, and 50% reversal also was calculated.

The other efficacy endpoints included summarised data of the following:

- Mean and individual values of dTT and ECT by time for Treated Patients with PD from the Central Laboratory.
- Maximum reversal, mean and individual values of TT and aPTT by time for Treated Patients with PD from the Central Laboratory
- Local lab aPTT, haemoglobin, haematocrit and platelets for all treated patients.
- Sum dabigatran (i.e., dabigatran and its pharmacologically active metabolites) and unbound sum dabigatran plasma concentrations as well as idarucizumab concentrations were determined using the same bioanalytical methodology as was used in the Phase I trials.

Other efficacy outcomes included: cessation of bleeding for patients in Group A and occurrence of major bleeding in patients in Group B. Such clinical evaluation and any clinical outcome events (stroke, MI, VTE) are discussed at the patient level when presented. For the complete and final CTR, clinical outcomes (stroke, MI, VTE, mortality) will be evaluated by an Endpoint Adjudication Committee. Both reported and adjudicated events are to be analysed.

[5] Reversal = $\frac{\text{predose coagulation test} - \text{minimum postdose coagulation test}}{\text{predose coagulation test} - 110\% \text{ ULN}} \times 100\%$

The ULN was determined using data from trials 1321.1 and 1321.2. It was calculated as the (arithmetic) mean + 2*standard deviation using all data collected prior to the dosing of DE and the data from patients who were on placebo as well as pre-dose data from idarucizumab alone treatment (as available). The 110% ULN value was chosen due to the higher variability among patients compared to volunteers. Values equal to or higher than 100% were interpreted as complete reversal of the anticoagulant effect.

7.1.5. Randomisation and blinding methods

Not applicable.

7.1.6. Analysis populations, sample size and statistical methods

This trial has a single treatment group with no control group. It was a case series with reversal of anticoagulation effect in each patient determined by pharmacodynamics parameters. The two patient groups (patients with uncontrolled or life-threatening bleeding that required urgent medical or surgical intervention and those requiring emergency surgery/procedures) were analysed separately, with an overall conclusion if possible. Overall assessment of efficacy was based on descriptive statistics, with confidence limits provided when appropriate.

7.1.7. Participant flow

From June 2014 until April 1, 2015, 123 patients were enrolled from 219 activated sites in 35 countries, including 5 patients from 26 US sites. All of the 123 patients in this analysis received the pre-specified 5 g dose of idarucizumab. There were 66 patients in Group A (bleeding) and 57 patients in Group B (surgery). The total planned observation time of this study is 3 months. Of 123 patients in this interim analysis, 32 (26%) are still in follow-up at the time of data cutoff with a minimum of 1 month observation. Sixty-two (50.4%) of the remaining 91 patients completed 3 months observation or did not (N=29, 23.6%); 29 (23.6%) patients did not complete the 3 months duration due to AEs (N=24, 19.5%), lack of compliance with the protocol (N=1, 0.8%), withdrawal of consent (N=1, 0.8%), or other reasons (N=3, 2.4%). Twenty-six of the 29 patients who did not complete the planned observation time died (2 deaths were classified as starting in screening). Overall, efficacy was evaluated in 90 patients with central laboratory assessment of efficacy (51 and 49 patients in Group A and B, respectively).

7.1.8. Major protocol violations/deviations

There was one major protocol violation. A patient was allocated to Group A based on an initial diagnosis of intracranial bleeding and was treated with idarucizumab. However, the initial diagnosis of bleeding was incorrect. Upon further investigation he was discovered to have metastatic melanoma in his brain with significant oedema. There was no bleed, therefore the patient was not eligible. The patient died 105 days later due to progression of the malignancy.

7.1.9. Baseline data

Majority of the patients in this study were male (52.8%) and White (85.4%) with median age of 77 years, median body weight of 72kg and median CrCl of 68.4ml/min. The primary indication for treatment with dabigatran etexilate was stroke prevention in patients with atrial fibrillation with 95% of patients in this interim analysis of the study being treated for this indication. The most common dose of dabigatran etexilate was 110 mg bid (65% of patients), reflecting the recruitment primarily outside the US, where 110 mg bid is not available. The median time between the last dose of dabigatran etexilate and the start of the first vial of idarucizumab was 15.6 hours, with a wide range from 1.5 to almost 94 hours. Approximately 1/3 of patients took their last dose less than 12 hours prior to treatment with idarucizumab, with 37% having the last dose between 12 and 24 hours and 26% between 24 and 48 h.

> *Comment: It is important to note that this estimate of time since the last dose of dabigatran etexilate is based on the patient-reported time of the last dose. The wide variability in clinical presentation and time of onset of the clinical events leading to treatment may also have contributed to the wide range of timing before treatment with idarucizumab.*

The patients treated with idarucizumab had a high frequency of co-morbidities. The frequency of risk factors associated with bleeding and stroke risk in a population with atrial fibrillation included 77% with hypertension, 39% with heart failure, 27% with diabetes, 31% with coronary artery disease, 28% with a previous history of stroke, 11.4% with a previous history of

TIA, and 8.9% with a previous history of systemic embolism. In addition, 4% had a prior major bleed and 11% had active cancer. The patients enrolled in this study (diagnosis of atrial fibrillation, median age of 77 years and poor renal function in many patients) represents a patient population with a high underlying risk for stroke, bleeding and death.

The details of the bleeding events leading to treatment in Group A are summarised in Table 3. The qualifying bleeds were almost all severe events based on several criteria. Based on the International Society for Thrombosis and Haemostasis (ISTH) classification of bleeding, 63 of the 66 bleeds were classified as either major or major and life-threatening. According to the GUSTO scale for bleeding severity, 47 bleeds were considered severe or life-threatening and 14 were evaluated as moderate. The TIMI bleeding classification classified 40 as TIMI Major and 2 as TIMI Minor. The remainder could not be classified due to the need for prebleed and subsequent haemoglobin values which were not always available. Ultimately, the judgment of the treating physician determined whether the patient qualified. There were 57 of 66 patients with either ongoing blood loss (N=39) or bleeding into a critical organ (N=18). In the remaining 9 patients, 1 was not assessable and in 8 continuing blood loss could not be determined. Of the 39 with ongoing blood loss, 24 were haemodynamically unstable. Surgical intervention occurred in 18 patients (27.3%) and 11 (16.7%) required use of i.v. inotropic agents for management of bleed-associated hypotension. The index events in the 66 patients in the bleeding subgroup were primarily gastrointestinal (N=27, 40.9%) or intracranial (ICH, N=24, 36.4%). Intramuscular (N=3, 4.5%), retroperitoneal (N=2, 3.0%), intra-pericardial (N=2, 3.0%), and intra-articular (N=2, 3.0%) bleeds also occurred. Bleeding was associated with trauma in 12 patients. The trauma was to the head in 10 of the 12 patients.

Table 3. Baseline bleeding assessment (Group A).

Characteristic	Group A
Number of patients with bleeding baseline	66 (100.0)
Bleeding locations [N(%)]	
Intracranial	24 (36.4)
GI	27 (40.9)
Intramuscular	3 (4.5)
Retroperitoneal	2 (3.0)
Intra-pericardial	2 (3.0)
Intraocular	0 (0.0)
Intraspinal	0 (0.0)
Intra-articular	2 (3.0)
Not yet identified	1 (1.5)
Other	11 (16.7)
Location of intracranial bleeds [N(%)]	
Subdural	9 (13.6)
Subarachnoid	6 (9.1)
Intracerebral	14 (21.2)
Type of GI bleeds [N(%)]	
Lower GI	8 (12.1)
Upper GI	10 (15.2)
Unknown	9 (13.6)
Patients with trauma [N(%)]	12 (18.2)
Blunt	11 (16.7)
Penetrating	1 (1.5)
Extremity	2 (3.0)
Torso	4 (6.1)
Head	10 (15.2)

Of the 57 patients allocated to the surgery/invasive procedure Group B, 3 patients did not undergo the planned surgery.

Only 90 of the 123 patients in this interim analysis had central laboratory data available for analysis. The demographics of the 90 patient subset were similar to that of the complete cohort

in terms of age, gender, weight, renal function, dabigatran use, medical history, baseline bleeding characteristics and type of surgery/invasive procedure.

The intravenous administration of idarucizumab was accomplished either as a spiked vial followed by gravity drip (41.5%), infusion pump (5.7%) or via a syringe (52.8%). The spiking technique was more frequent in Group A while the syringe was more frequent in Group B. The median time for administration was 5 minutes per vial (range 1-16 minutes), with a median total elapsed time between start of the first vial of idarucizumab until the end of the second vial of 19 minutes (range 5-52 minutes). In addition to the 123 patients in this analysis, there were 2 patients after the cutoff date who received a second 5 g dose within 24 hours.

7.1.10. Results for the primary efficacy outcome

For the 90 patients where analysis of efficacy was based on central laboratory data, not all patients had baseline clotting tests with values that were above the upper limit of normal. For the primary efficacy endpoint calculated using ECT or dTT, between 71.8 and 92.2% of patients could be included in the efficacy analysis, depending on the clotting test used and the subgroup (Group A or Group B). Normal clotting times or missed baseline samples were not included in the efficacy analysis. However, all patients in the study had detectable levels of dabigatran at baseline, with values as low as 5.5 ng/mL which confirmed that all patients had taken dabigatran etexilate.

The primary endpoint in this study was the central laboratory determination of the maximum reversal of the anticoagulant effect of dabigatran in the first 4 hours, as determined by ECT or dTT. These analyses were based on the 90 patient subset with central lab data. The protocol specified a calculation of maximum reversal based upon 110% of the laboratory upper limit of normal (ULN) in anticipation of a higher variability in patients compared to volunteers (lab normals had been calculated based on volunteer data). However, similar data were obtained using 100% compared to 110% ULN so the more rigorous 100% was used as the basis of reversal calculations.

At entry, the dTT was normal in 22 patients, of whom 9 also had normal ECT. Therefore, percentage reversal of either test with idarucizumab could be determined in 68 (40 in Group A and 28 in Group B) and 81 (47 in Group A and 34 in Group B) of the 90 patients, respectively.

The maximum reversal of ECT or dTT in the first 4 hours was the primary endpoint. The median maximum reversal in Group A and B patients was 100% (95% Confidence Interval, 100-100) for both the dTTand ECT; the narrow confidence interval may be due to the fact that most of the patients (>89%) achieved complete reversal. The reversal was evident immediately after administration of the first vial. The dTT was normalised[6] in 97.5% and 92.9% of evaluable patients in Groups A and B, respectively, whereas the ECT was normalised in 89.4% and 88.2% of evaluable patients in Groups A and B, respectively. Differences in assay sensitivity (ECT is more sensitive to dabigatran than dTT) may have contribute to the observed differences. At 12 and 24 hours, dTTs were below the upper limit of normal in 90.2% and 80.7% of available patients, respectively, while the ECTs were below the upper limit of normal in 71.6% and 54.3% of available patients, respectively. Similar results for the determination of maximum reversal were obtained with the aPTT measured in the central laboratory. Thrombin time (TT) measurements also showed similar results compared to the other clotting tests. Median maximum reversal was 100% (95%CI, 100-100). A formal evaluation of duration of reversal was not performed. However, at the planned timepoints, the median clotting times for dTT and ECT were below the 100% ULN threshold.

The 22 patients with normal baseline clotting tests had better renal function compared with the 68 patients with elevated baseline clotting tests (dTT), (median creatinine clearances of 67 and

[6] Normalisation of clotting tests is defined as those tests with values equal to or below the upper limit of normal.

48 mL/min, respectively) and a longer time since the last dose of dabigatran (median 30.3 and 12.8 hours, respectively). Among the 11 Group A patients with normal baseline clotting tests, a higher proportion had intracranial bleeding compared with the 38 Group A patients with elevated baseline tests (63.6% and 27.5%, respectively). There was 1 death and 2 thrombotic events among the 22 patients with normal clotting tests at baseline, and 17 deaths and 3 thrombotic events in the 68 patients with elevated baseline clotting tests.

7.1.11. Results for other efficacy outcomes

Data on sum (total) dabigatran concentrations were available for 89 of 90 patients. The median total dabigatran concentration at baseline was 114.0 ng/mL with a range of 5.5 to 3600 ng/mL. The median concentration is slightly higher than the median trough concentration of 93 ng/mL dabigatran in RE-LY with a dose of 150 mg bid. The highest concentration measured in RE-LY patients was 1000 ng/mL. There are 2 patients in this interim analysis with concentrations exceeding the highest seen in RE-LY and the reason for such high concentrations is not known. Both patients were in Group B (surgery) and neither experienced any bleeding before surgery. Haemostasis during surgery in these patients was normal Immediately following administration of idarucizumab, the median concentration of unbound dabigatran, i.e. dabigatran not bound to thrombin, plasma proteins, or idarucizumab, was below 1 ng/mL (BLQ) and remained so over the 24 h duration of measurement. However, there were 19 of 89 patients (21%) with a re-appearance of unbound dabigatran >20 ng/mL at one or more of the time points of 4, 12 or 24 hours after treatment. At 4 hours, there were 3 patients >20 ng/mL.[7] At 12 hours there were 6 patients >20 ng/mL, of which 2 had also exceeded the threshold at 4 hours, and at 24 hours there were 16 patients >20 ng/mL, of which 4 exceeded the threshold at 12 hours. Eleven of these 19 patients had unbound dabigatran concentrations in excess of 50 ng/mL.

The re-elevation of unbound dabigatran was positively correlated with higher baseline concentrations of unbound dabigatran as well as with poor renal function. The clinical significance of the late reappearance of unbound dabigatran is not clear, unless there are clinical signs of bleeding or a need for emergency surgery or intervention. Although not received before the cut-off for the interim analysis, there were 2 patients who showed evidence of elevated clotting tests and re-bleeding after 5 g of idarucizumab who received a second 5g dose. In both patients, the re-bleeding stopped and the clotting parameters normalised after the second 5 g dose. The parallel decrease of unbound dabigatran concentrations with normalisation of the clotting parameters (and the parallel increase of concentrations with re-elevation of clotting parameters) confirms the reversal of dabigatran induced anticoagulant effects by idarucizumab.

> *Comments: The reversal of the anticoagulant effect of dabigatran by idarucizumab was demonstrated in this patient population, based on local or central biomarkers. The PK/PD data obtained were consistent with observations made in healthy volunteers in Phase 1 studies.*

Clinical outcomes

Hospitalisation/ ICU stay

For the 123 treated patients, data on hospitalization was available for 112 and ICU stay was recorded for 116. The duration of hospitalisation was calculated based only on dates, not times and the median duration was 8 calendar days (range 2-93). The median duration for ICU stay was 0 days (range: 0 to 44). There did not appear to be relevant differences between Groups A and B.

[7] A concentration of unbound sum dabigatran of 20ng/mL is estimated to be at or near a threshold where changes in clotting tests can be observed.

Bleeding status

In Group A, bleeding cessation was determined by the investigator/treating physician[8] in 48 of 66 patients (73%) with no assessment possible for the other 18 patients. For 44 of 48 assessable patients, bleeding stopped within 72 h. The median time to stop bleeding was 9.8 hours (range: 0.2 h to 62 days).

In Group B, intra-operative status of bleeding was determined in 52 patients. For 48 patients (92.3%), the surgeon judged there to be normal haemostasis. For 3 patients (5.8%), mildly abnormal intraprocedural haemostasis (e.g. slight oozing) occurred and 1 patient (1.9%) was judged to have moderately abnormal haemostasis (e.g. controllable bleeding). This resulted in 1 bleed reported within 24 hours post-surgery, classified as ISTH minor, TIMI minimal, and GUSTO mild.

Use of blood products

Usage of blood products was more frequent in the Group A patients (68.2%) compared to Group B (40.4%) and occurred more frequently after idarucizumab treatment than before treatment. The most frequently used product was packed RBCs, used in 41.5% of all patients (59.1% of Group A patients), with FFP (fresh frozen plasma) the second most frequently used blood product, used in 24.4% of all patients. Platelets and volume expanders were each used in 13.6% of Group A patients. Use of other products, including PCCs (5 of 123 patients, 4.1%) was relatively infrequent. No Factor VIIa was administered.

> *Comment: The sponsors suggest that the early findings for the clinical endpoints of bleeding reduction and minimal blood in operative field suggest that positive clinical outcomes can be anticipated with idarucizumab reversal of dabigatran-induced anticoagulation. However, due to the open-label, single treatment group design and the heterogeneity of the patient population, definitive conclusions on the clinical outcomes are not possible. Overall, there is inadequate data to enable evaluation of idarucizumab on clinical outcomes at this stage.*

Restarting anticoagulant therapy

Anticoagulant or antithrombotic therapy was re-started in 96 patients (47 in Group A and 49 in Group B). Dabigatran was re-started in 17 (25.8%) of the Group A patients and 34 (59.6%) of the Group B patients. Dabigatran re-start was preceded by bridging therapy in 8 of the 17 patients in group A and 25 of 34 patients in group B. The median time to re-start any anticoagulant/antithrombotic/antiplatelet therapy was 4.6 days for group A and 1.3 days for group B patients. Dabigatran re-start took 17.5 days in group A and 6.5 days in group B. The management of re-starting antithrombotic therapy differed for bleeding versus surgery patients. Dabigatran was less likely to be re-started in bleeding patients compared to surgical patients and the time to re-start was much longer in bleeding patients (17.5 versus 6.5 days). In general the time to re-start of any antithrombotic was much faster in surgery patients compared to bleeding patients.

7.2. Other efficacy studies

Results of the 3 Phase 1 studies (1321.1, 1321.2 and 1321.5) are discussed and a comparison and analysis of results across these 3 Phase 1 studies is also provided below.

[8] Cessation was subjective and based upon whatever the investigator could visualise or measure. Sometimes tests, e.g. CT scans or MRIs, were not repeated for several days. In addition to this assessment, severity of bleeding including hemodynamic status, was determined and bleeds were rated using international bleeding scales (ISTH, GUSTO, TIMI).

7.3. Analyses performed across trials (pooled & meta analyses)

7.3.1. Comparison and analysis of results across Phase 1 studies:

7.3.1.1. Subject and exposure in the Phase 1 studies

Of the 283 subjects on active treatment in the 3 Phase 1 studies (1321.1, 1321.2 and 1321.5), 117 subjects were pre-treated with DE. Similar proportions of subjects from each Phase I study contributed to the treatment group DE+Ida. 70 subjects were treated with DE+Placebo.[9] Individual subjects were grouped by the total idarucizumab doses administered following dabigatran etexilate pre-treatment: <2.5 g, ≥2.5 g to <5 g, 5 g, >5g to 8 g, and placebo treatment. The highest dose of 8 g was administered only to subjects without DE pre-treatment. 50 subjects received idarucizumab in the range of 1 g to <2.5 g, 23 subjects received ≥2.5 g to 5 g. 35 subjects were treated with the target clinical dose of 5 g idarucizumab and 9 subjects >5 g to ≤8 g. Overall, 9 subjects (7.7%) were treated with 2 single infusions of idarucizumab given 15 min apart and 9 subjects (7.7%) received 2 single infusions of idarucizumab given 60 min apart. Re-exposure to idarucizumab (2 months after the first dose) occurred in 6 subjects (5.1%) in trial 1321.2. In all 3 Phase 1 studies, all randomised subjects were also treated with at least 1 dose of study medication and all completed the planned observation time.

7.3.1.2. Baseline demographics and characteristics

The inclusion criteria differed between the 3 Phase I trials regarding age, sex, and renal impairment, resulting in differences between the treatment groups when pooling all 3 Phase I studies. The pooled Phase I trials included more men than women; female subjects were only included in trial 1321.2 but not in the other Phase I trials. The majority of the subjects had an age of ≥19 to <45 years which reflects the main inclusion criterion for studies 1321.1 and 1321.5. 56/70 (80.0%) of the subjects treated with DE+placebo and 79/117 (67.5%) treated with DE+idarucizumab were White (Trials 1321.1 and 1321.2). 13/70 (18.6%) in the DE+placebo group and 37/117 (31.6%) in the DE+idarucizumab group were Japanese Asians (Trial 1321.5). Demographic characteristics regarding weight and BMI were balanced across the treatment groups. Most female subjects (10 of 19) received a total dose of 5 g, whereas none were in the highest dose group. The mean age among dose groups varied between 29.9 and 54.4 years. The highest mean age was observed in subjects receiving 5 g idarucizumab. Overall, 30 subjects aged 65- 80 years were treated with idarucizumab, whereas no subject was above 80 years. In the pooled analysis, the majority of subjects (DE+placebo 51/70, 72.9%; DE+idarucizumab 97/117, 82.9%) had normal renal clearance the pooled analysis of the DE+idarucizumab group included 19/117 subjects (16.2%) with mild renal impairment and 1 subject (0.9%) with moderate renal impairment, and in the DE+placebo group 18 subjects (25.7%) and 1 subject (1.4%), respectively. 7 and 12 subjects with mild renal impairment received a dose of 1 and 5 g, respectively, the subject with moderate renal impairment received 5 g idarucizumab.

7.3.1.3. Efficacy in terms of reversal of dabigatran-induced anticoagulation in Phase 1 studies

Mean baseline coagulation times in the absence of dabigatran as well as at steady state just before administration of idarucizumab were similar for the individual assays and across dose groups. However, coagulation times of all assays appeared slightly lower prior to administration of the highest idarucizumab dose (>5 g to ≤8 g).

Across all dose groups and using both thresholds (100% and 110% ULN within 4 hours since start of idarucizumab), 100% of subjects were detected with complete reversal by the dTT assay and all but one subject (97.1%) were detected with complete reversal based on the ECT assay.

[9] In the cross-over design study 1321.2, subjects received both idarucizumab and placebo treatments, thus these individual subjects are counted twice in the combined analysis.

Similar results were obtained for the TT and aPTT parameters. Subjects detected without complete reversal for one coagulation assay were usually not confirmed by the other assays. "Non-reversal" was generally due to the pre-dose measurement below the ULN.

Across all parameters and independent of the used ULN, complete reversal was essentially observed at the end of the 5 min idarucizumab infusion, i.e. median time to reversal was about 5-6 min depending on the actual time the first post-dose sample was drawn (Table 7.2.5, p**Error! Bookmark not defined.**). Consistently over the primary parameters dTT and ECT, and supported by aPTT, median duration of reversal was 72 hours (i.e. length of the observation period) for idarucizumab doses of 2.5 g or more at the dabigatran concentrations achieved in the Phase I trials. This was independent from the used ULN. Mean duration was somewhat shorter for 100% ULN compared to 110% ULN, however mean duration of complete reversal following idarucizumab doses >2.5 g was still >50 hours for these three coagulation assays (dTT, ECT and aPTT). Duration of complete reversal based on TT was shorter compared to the other coagulation assays in all dose groups.

7.3.1.4. Effect of idarucizumab on unbound sum dabigatran in Phase 1 studies

Before idarucizumab infusion, dabigatran concentrations were similar across groups. Following placebo infusion, gMean unbound sum dabigatran concentrations were at levels around 150 ng/mL and returned over a time frame of about 24 h to levels of approximately 25 ng/mL. In contrast, following i.v. infusion of idarucizumab doses of 2.5 g or higher, gMean unbound sum dabigatran concentrations were reduced to levels close to the LLOQ (1 ng/mL) and remained at these concentrations over the entire observation period.

7.3.1.5. Comparison of results from Phase 1 studies in subgroups based on sex, age, race and renal impairment

Male and female subjects were included in study 1321.2. There was no obvious difference in the reversal of dabigatran anticoagulation between males and female subjects. Administration of a total dose of 5 g idarucizumab resulted in sustained reversal of coagulation times.

Reversal of dabigatran mediated anticoagulation was comparable between young and elderly subjects. Administration of a total dose of 5 g idarucizumab resulted in sustained reversal of coagulation times in both Japanese and Caucasian subjects.

Subjects with mild or moderate renal impairment were included in study 1321.2. Decreased renal function had no obvious effect on the reversal of dabigatran mediated anticoagulation.

7.3.2. Persistence of efficacy and/or tolerance effects:

Idarucizumab is intended for single use in patients taking dabigatran etexilate, either when uncontrollable/ life-threatening bleeding or urgent surgery/procedures require rapid reversal of dabigatran-induced anticoagulation. Therefore, the term "persistence of efficacy" in the sense of a long term medication does not apply. However, the following related aspects are summarised below.

7.3.2.1. Sustainability

Sustainability of the effect was defined as mean coagulation times of the respective assay remain below ULN during the entire respective observation period. Consistently over the primary parameters dTT and ECT, and supported by aPTT, median duration of reversal was 72 hours for idarucizumab doses of 2.5 g or more. This was independent from the used ULN. Mean duration was somewhat shorter and reduced for 100% ULN compared to 110% ULN, however mean duration of complete reversal following idarucizumab doses >2.5 g was still >50 hours for these three coagulation assays.

7.3.2.2. Re-administration of dabigatran etexilate

Most patients treated with dabigatran etexilate have an indication for long-term anticoagulation. However, conditions leading to idarucizumab administration will usually lead to interruption of dabigatran therapy. After the treatment of the emergency, provided the clinical situation allows and adequate haemostasis has been established, restart of DE therapy can be considered. Some idarucizumab may remain circulating for up to 24 hours after infusion (less than 1% of the dose in subjects with normal renal function).

In study 1321.2, re-administration of DE after idarucizumab infusion in the group of healthy subjects aged 45-64 years investigated whether normal dabigatran anticoagulation effects could be re-established after administration of idarucizumab. In the group of healthy subjects aged 45 to 64 years receiving either 2.5 or 5 g idarucizumab, DE 220 mg BID treatment was restarted 24 h after the end of the idarucizumab infusion and continued to a total of 5 doses to investigate whether a normal DE treatment with normal dabigatran anticoagulation effects can be re-established after administration of idarucizumab. A comparison of trough (Cpre,ss) and 2 h (C1.92,ss) plasma concentrations of sum dabigatran before the infusion of idarucizumab or placebo with those after restart of DE administration (Cpre,ss,12) and C2,ss,12) revealed no effect on exposure to sum dabigatran 24 h prior to infusion of idarucizumab. Pre-treatment with DE and restart of DE treatment 24 h after infusion of placebo or idarucizumab to healthy subjects aged 45 to 64 years resulted in similar trough and 2 h post-dose values of dTT, ECT, aPTT, and TT ratio to baseline.

7.3.2.3. Re-dosing of idarucizumab

A small fraction of patients may be treated a second time with idarucizumab, e.g. months or years after the first treatment. The exploratory re-exposure to idarucizumab after a period of time relevant for potential anti-drug antibody (ADA) formation should help to provide efficacy safety and tolerability data important for a repeated exposure to idarucizumab. This was evaluated in study 1321.2 which explored the efficacy of idarucizumab when given the second time. Approximately 2 months after the first infusion of 2.5 g idarucizumab, 6 healthy volunteers aged 45 to 64 years were re-exposed to 2.5 g idarucizumab after pre-treatment with DE 220 mg BID for 3 days and a single dose on day 4. Plasma concentration time profiles of idarucizumab were almost identical and could be detected up to 24 h. Similar plasma concentration time profiles for unbound sum dabigatran concentrations and comparable reversal of dabigatran-induced anticoagulation were observed, suggesting similar effectiveness of idarucizumab after first and second administration. The analyses for reversal assessed by dTT and ECT are consistent with the results obtained after the first infusion of 2.5 g idarucizumab. Of note, none of the six subjects reexposed to idarucizumab subjects was tested positive for anti-idarucizumab ADAs prior to either of the idarucizumab administrations. One subject had treatment-emergent ADAs in the 3-months follow-up visit.

> *Comments: Overall, the results suggest that there was no difference in reversal of dabigatran-induced anticoagulation between the first infusion of idarucizumab and re-exposure approximately 2 months later.*

7.4. Evaluator's conclusions on efficacy

Efficacy of idarucizumab for the proposed indication:

> *When rapid reversal of the anticoagulant effects of dabigatran is required:*
>
> - *for emergency surgery/urgent procedures;*
> - *in life-threatening or uncontrolled bleeding*

was assessed, based on the reversal of dabigatran induced anticoagulation as measured by biomarker tests and the level of unbound sum dabigatran.

The selection of the clinical dose for patients and the demonstration of dose-response are based on biomarker response to different doses of idarucizumab and the concomitant reduction of the unbound sum dabigatran. PK/PD modelling was used to further substantiate dosing considerations. Clinical outcome data were not used in the estimation of the dosing. The recommended dose for patients is 5 g idarucizumab.

> *Comments: Overall, the combined analysis of the three Phase 1 studies supports the proposed total dose of 5 g. It provides evidence that idarucizumab administered at doses of 2.5 g or higher achieves complete reversal in 100% of subjects within about 5 to 6 min after start of infusion. The effect was durable with a median duration of reversal of 72 h. The reversal of anticoagulant effect based on biomarkers was substantiated by pharmacokinetic observations of low plasma levels of unbound sum dabigatran. The assay of unbound sum dabigatran provides an important, independent verification of reversal in addition to the coagulation assays. For example, the sub-therapeutic dose of 1g idarucizumab, after initial complete reversal, shows a rise in unbound sum dabigatran in parallel with a partial return of anticoagulant effect*

In the ongoing Phase III Study 1321.3 (RE-VERSE AD), clinical data were available for 123 patients and central laboratory data for assessment of efficacy were available for 90 patients: 51 patients in Group A (bleeding) and 49 patients in Group B (surgery). Efficacy assessment in this study is based primarily on changes in clotting tests after administration of idarucizumab. Each patient served as his own control so an extent of reversibility could be calculated. Verification that changes in clotting tests reflected the binding and inactivation of dabigatran was accomplished by simultaneous HPLC/MS measurement of unbound sum dabigatran in the same samples. Clinical outcomes such as time to cessation of bleeding, level of haemostasis during surgery, thrombotic events and deaths were also recorded.

In a patient population treated with dabigatran who may need emergency surgery or treatment for uncontrolled bleeding, idarucizumab achieved a median maximum reversal of the anticoagulant effect of dabigatran within the first 4 h of 100%. Complete reversal of the clotting tests was achieved within minutes and the reversal was sustained in approximately 80% of the patients for 24 h. This was confirmed by the fact that unbound dabigatran decreased to below the lower limit of quantitation in parallel with the reduction in clotting. Even in the subset of patients where clotting tests were above the ULN at 12 or 24 h, the reductions in anticoagulant effect were still substantial. These findings confirm that 5 g of idarucizumab represents an overwhelming dose which is sufficient to reverse the anticoagulant effect of dabigatran in almost all patients. This reversal of elevated anticoagulation tests in dabigatran treated patients is a surrogate for clinical efficacy.

A clinical benefit of this reversal depends on the individual patient situation. In this interim analysis, it was difficult to objectively determine the efficacy in stopping bleeding because the bleeds were frequently not visible and difficult to assess, for example, in the case of ICH, some gastrointestinal bleeds or retroperitoneal bleeds. Cessation was subjective and based upon whatever the investigator could visualise or measure. Despite these limitations, bleeding did stop in 44 of 48 evaluable patients within 72 h and the median time to cessation of bleeding was 9.8 h. In the case of emergency surgery, 33 out of 36 evaluable patients had normal haemostasis during surgery. The very short time between treatment with idarucizumab and start of surgery (median 1.7 h) also allowed rapid surgical/procedural intervention. However, in this single cohort study there is no control group so any conclusions based solely on clinical outcomes are limited at best.

8. Clinical safety

8.1. Studies providing safety data

8.1.1. Pivotal efficacy studies

Study 1321.3 was the only Phase III study conducted in the target patient population.

The following safety data was collected in the Phase III study:

- General adverse events (AEs): All AEs occurring before infusion of the first vial idarucizumab were assigned to the screening period. All AEs recorded after the first vial of idarucizumab and until 5 days after the last dose of idarucizumab were assigned to the treatment period. All AEs occurring thereafter until the cut-off date were assigned to the post-treatment period. In addition, AEs with an onset date before start of the trial treatment but with worsening in intensity during the treatment were also assigned to the treatment period. Treatment-emergent AEs are presented for the treatment period (including a washout period of 5 days after last administration of study medication) and the post-treatment period (starting 6 days after last administration of study medication).

Worsening of the underlying disease or of other pre-existing conditions was recorded as an (S)AE in trial 1321.3. Worsening of vital signs, ECG, physical examination and laboratory test results was recorded as an (S)AE, if they were judged clinically relevant by the investigator. Hepatic injury was defined as pre-specified significant AE. For patients with normal liver function at baseline, this was defined as an elevation of AST and/or LT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample. For patients with impaired liver function tests at baseline, hepatic injury was defined as follows: An elevation of AST and/or ALT >3x ULN combined with an elevation of total bilirubin >2x ULN measured in the same blood sample if transaminases were within normal range; doubling of transaminases combined with an elevation of total bilirubin >2x ULN measured in the same blood sample if transaminases were >2x ULN at baseline.

8.1.2. Pivotal studies that assessed safety as a primary outcome

None.

8.1.3. Dose-response and non-pivotal efficacy studies

Safety data from the three Phase I studies (1321.1, 1321.2 and 1321.5) was pooled and additional information on the individual studies was provided when appropriate. Safety parameters assessed in the Phase I studies included:

- All AEs with an onset any time following the first dose of study drug were assigned to the preceding treatment received. In the pooled analyses of the 3 Phase I trials, all AEs occurring up to 5 days after the last application of trial medication were assigned to the treatment period. All AEs occurring thereafter were assigned to the post treatment period for the pooled analysis of the 3 Phase I studies. Drug related AEs, deaths/ SAEs, discontinuations due to AE and certain pre-specified AEs. The number of subjects with pre-specified AEs was summarised descriptively for treated subjects based on the individual definitions on trial level.

In trial 1321.1, the following AEs were defined as pre-specified significant AEs: Drop in SpO2 <90%, Increase in body temperature >38°C; Drop of systolic blood pressure <90 mmHg, Increase in resting heart rate >100 bpm; Any symptoms of respiratory distress.

The crossover trial 1321.2 categorised the following AEs as pre-specified significant AEs: Hepatic injury with an elevation of AST and/or ALT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample; Increase in body temperature

>38°C; Drop of systolic blood pressure <90 mmHg; Increase in heart rate >100 bpm; Any symptoms of respiratory distress.

In the Japanese trial 1321.5, hepatic injury was defined as pre-specified significant AE for subjects with normal liver function at baseline if they had during the trial an elevation of AST and/or ALT ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample.

8.2. Patient exposure

In the ongoing Phase III Study 1321.3, all of the 123 patients in the interim analysis (dated June 2015) received the pre-specified 5 g dose of idarucizumab. There were 66 patients in Group A (bleeding) and 57 patients in Group B (surgery). The total planned observation time of this study is 3 months. Of 123 patients in this interim analysis, 32 (26%) are still in follow-up at the time of data cut-off with a minimum of 1 month observation. Sixty-two (50.4%) of the remaining 91 patients completed 3 months observation or did not (n = 29, 23.6%); 29 (23.6%) patients did not complete the 3 months duration due to AEs (n = 24, 19.5%), lack of compliance with the protocol (n = 1, 0.8%), withdrawal of consent (n = 1, 0.8%), or other reasons (n = 3, 2.4%).

The median time between the last dose of dabigatran etexilate and the start of the first vial of idarucizumab was 15.6 h, with a wide range from 1.5 to almost 94 h. Approximately 1/3 of patients took their last dose less than 12 h prior to treatment with idarucizumab, with 37% having the last dose between 12 and 24 h and 26% between 24 and 48 h. The IV administration of idarucizumab was accomplished either as a spiked vial followed by gravity drip (41.5%) or infusion pump (5.7%), or via a syringe (52.8%). The spiking technique was more frequent in Group A while the syringe was more frequent in Group B. The median time for administration was 5 minutes per vial (range 1-16 minutes), with a median total elapsed time between start of the first vial of idarucizumab until the end of the second vial of 19 minutes (range 5-52 minutes). In addition to the 123 patients in this analysis, there were 2 patients after the cut-off date who received a second 5 g dose within 24 h.

There were 283 treated subjects in the 3 Phase I studies. Trials 1321.1 and 1321.2 were conducted in Belgium at the same clinical site while the single centre study 1321.5 was performed in Japan. Of these 283 treated subjects, 224 subjects were treated with idarucizumab and 105 subjects received placebo (regardless of dabigatran etexilate pretreatment). Study 1321.1 contributed half of the subjects (52.7%) to the treatment group 'Ida/DE+Ida' while similar proportions of subjects from Studies 1321.2 and 1321.5 were treated with Ida/DE+Ida. Overall, 141 of 283 treated subjects received pre-treatment with DE, with a contribution of similar proportions of subjects across studies (each approximately one third). All 46 treated subjects in the crossover trial 1321.2 were pretreated with DE before infusion of idarucizumab or placebo whereas about 30% (1321.1) and 60% (1321.5) of the subjects in the respective study received pretreatment with DE. In the combined Phase I studies, a similar number of subjects were either treated only with idarucizumab (107 subjects) or with DE+Ida (117 subjects). In the pooled Phase I trials, the most frequently applied dose of idarucizumab (Ida/DE+Ida) was in the range of ≥1 g to <2.5 g for 41.1% of all subjects, followed by ≥2.5g to <5 g idarucizumab for 21.0% of subjects. Similar proportions of subjects received 5 g idarucizumab (15.6%) or higher doses of >5 g to 8 g idarucizumab (12.1%), based on all subjects receiving idarucizumab with or without DE pretreatment. Among idarucizumab treated subjects who were pre-treated with DE (DE+Ida), the most frequently applied dose of idarucizumab (DE+Ida) was still in the range of ≥1 g to <2.5 g (42.7%) while the proportions of subjects who received 5 g DE+Ida were higher (29.9%) than for the dose range ≥2.5g to <5 g DE+Ida (19.7%).

The vast majority of subjects received idarucizumab as single dose infusion (DE+Ida: 79.5%, Ida/DE+Ida: 89.3%). Overall, 9 subjects (DE+Ida: 7.7%, Ida/DE+Ida: 4.0%) were treated with 2

single infusions of idarucizumab given 15 min apart and 9 subjects (DE+Ida: 7.7%, Ida/DE+Ida: 4.0%) received 2 single infusion of idarucizumab given 60 min apart. Re-exposure to idarucizumab (2 months after the first dose) occurred in 6 subjects (DE+Ida: 5.1%, Ida/DE+Ida: 2.7%) in trial 1321.2.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Phase 3 study 1321.3 (interim analysis)

At least one AE was reported for 103 of 123 treated patients (83.7%), 59 in Group A (89.4%) and 44 in Group B (77.2%). Overall, the reported events were serious in 53 patients (43.1%), 31 in Group A (47%) and 22 in group B (38.6%). Fatal events occurred in 26 patients, 13 in each group (Table 4).

Table 4. AEs overall summary, treated patient set, Study 1321.3.

	Group A		Group B		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	66	(100.0)	57	(100.0)	123	(100.0)
Subjects with any AE	59	(89.4)	44	(77.2)	103	(83.7)
Subjects with severe AEs	23	(34.8)	16	(28.1)	39	(31.7)
Subjects with investigator defined drug-related AEs	4	(6.1)	1	(1.8)	5	(4.1)
Subjects with other significant AEs (according to ICH E3)	0	(0.0)	0	(0.0)	0	(0.0)
Subjects with AEs leading to discontinuation of trial drug	0	(0.0)	0	(0.0)	0	(0.0)
Subjects with significant AEs (pre-specified events)	0	(0.0)	0	(0.0)	0	(0.0)
Subjects with serious AEs	31	(47.0)	22	(38.6)	53	(43.1)
Fatal*	12*	(18.2)	12*	(21.1)	24*	(19.5)
Immediately life-threatening	1	(1.5)	1	(1.8)	2	(1.6)
Disability/incapacitation	1	(1.5)	1	(1.8)	2	(1.6)
Required hospitalisation	11	(16.7)	9	(15.8)	20	(16.3)
Prolonged hospitalisation	7	(10.6)	6	(10.5)	13	(10.6)
Congenital anomaly	0	(0.0)	0	(0.0)	0	(0.0)
Other	4	(6.1)	4	(7.0)	8	(6.5)

*Does not include 2 deaths, 1 each in Groups A and B, where event started in Screening (pre-treatment) and patient died after treatment (see Section 3.1.1. for list of all deaths).
A patient may be counted in more than one seriousness criterion.
Percentages are calculated using total number of subjects per treatment as the denominator.
MedDRA version used for reporting: 17.1

8.3.1.2. Phase 1 studies

During the treatment period, no difference in overall AE frequencies was observed between idarucizumab-treated subjects (Ida/DE+Ida: 24.6%) and placebo-treated subjects (placebo/ DE+placebo: 24.8%). When comparing only subjects pretreated with DE, the proportions of subjects with AEs were very similar in the DE+Ida (22.2%) and DE+placebo (20.0%) groups. Regarding subjects who did not receive pretreatment with DE, slightly more placebo-treated subjects (34.3%) had AEs compared with idarucizumab-treated subjects (27.1%). Overall, subjects were most frequently reported with AEs during pretreatment with DE (30.5%) before infusion of idarucizumab or placebo (Table 5).

Table 5. AEs overall summary for the pooled Phase I studies during the treatment period – TS.

	DE[1]	Placebo		Idarucizumab		Total	
		Placebo alone	DE+placebo	Ida alone	DE+Ida	Placebo/ DE+placebo	Ida/ DE+Ida
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of subjects	141 (100)	35 (100)	70 (100)	107 (100)	117 (100)	105 (100)	224 (100)
Subjects with any AEs	43 (30.5)	12 (34.3)	14 (20.0)	29 (27.1)	26 (22.2)	26 (24.8)	55 (24.6)
Subjects with drug-related AEs	6 (4.3)	3 (8.6)	4 (5.7)	3 (2.8)	4 (3.4)	7 (6.7)	7 (3.1)
Subjects with AEs leading to discontinuation of trial drug	0	0	0	0	0	0	0
Subjects with other significant AEs (ICH E3)	0	0	0	0	0	0	0
Subjects with significant (prespecified) AEs	0	0	0	0	0	0	0
Subjects with severe AEs	0	0	0	0	0	0	0
Subjects with SAEs	0	0	0	0	0	0	0

Subjects from the crossover trial 1321.2 are counted in more than 1 treatment group.

[1] All subjects in trial 1321.2 and some subjects in trials 1321.1 and 1321.5 were pretreated with DE before infusion of idarucizumab/placebo. These subjects are counted in both DE and their respectively randomised treatment groups.

In the pooled Phase I studies, the intensity of AEs was mostly assessed as mild, with similar frequencies across treatment groups (DE pretreatment: 29.8%, placebo/DE+placebo: 23.8%, Ida/DE+Ida: 23.7%). Very few subjects had AEs of moderate intensity; they were documented with very similar frequencies across treatment groups (DE pretreatment: 0.7%, placebo/DE+placebo: 1.0%, Ida/DE+Ida: 0.9%). None of the AEs during the treatment period was classified as severe.

Considering only subjects pretreated with DE, no clinically relevant difference was noted in AE frequencies of mild AEs between placebo-treated subjects (DE+placebo) and the different idarucizumab dose categories. For AEs of moderate intensity, 1 of 9 subjects (11.1%) in the >5 g to ≤8 g idarucizumab dose category was reported with moderate asthenia. When taking into account only subjects who received DE pretreatment, the AE frequencies were similar in placebo-treated subjects and in idarucizumab-treated subjects who received idarucizumab doses up to 5 g in the 3 dose categories of <2.5 g, 2.5 g to <5 g, and 5 g. The AE frequencies were slightly higher in the smallest dose group receiving the highest idarucizumab dose of >5 g to ≤8 g (3 of 9 subjects, 33.3%). During the treatment period, the most common AEs on idarucizumab (Ida/DE+Ida) were headache (12 subjects, 5.4%), skin irritation (6 subjects, 2.7%), dizziness (5 subjects, 2.2%), and back pain (4 subjects, 1.8%). Nasopharyngitis, diarrhoea, and constipation were reported by 3 subjects (1.3%) in the Ida/DE+Ida group; all other AEs were reported by less than 1% in the Ida/DE+Ida group (at most 2 subjects on preferred term level). The most frequent AEs reported after infusion of idarucizumab were very similar to those documented for placebo-treated subjects. During pretreatment with DE and before infusion of idarucizumab or placebo, the most common AEs were headache (11 subjects, 7.8%), presyncope (5 subjects, 3.5%); abdominal discomfort, diarrhoea, and nausea were reported by 4 subjects each (2.8%). Epistaxis, abdominal pain, and haematuria were documented for 3 subjects each (2.1%) during pretreatment with DE; all other AEs were reported by at most 2 subjects (1.4%) of subjects on preferred term level. The most frequent AEs for idarucizumab-treated subjects were headache and skin irritation. Headache was reported more frequently by idarucizumab-treated subjects (Ida/DE+Ida: 5.4%) than for placebo-treated subjects (placebo/DE+placebo: 1.9%), however, the highest frequency of subjects with headache was noted during pretreatment with DE (7.8%) before infusion of idarucizumab or placebo. When considering only subjects with DE pretreatment, no clinically relevant differences in AE frequencies were observed in placebo-treated subjects and idarucizumab-treated subjects. Asthenia was reported by 2 subjects treated with idarucizumab; one (11.1%) of these subjects received an idarucizumab dose of 2.5 g to <5 g and 1 subject (11.1%) was treated in the highest idarucizumab dose category of >5 g to

≤8 g. Epistaxis, muscle spasms, and nasopharyngitis were documented for each 1 subject (11.1%) in the highest idarucizumab dose category of >5 g to ≤8 g. For the idarucizumab-treated subject, the epistaxis lasted 2 min and started 2 days after infusion of 5 g+2.5 g idarucizumab. Subjects on placebo (pretreated with DE) were also reported with epistaxis (1 subject, 1.4%) and nasopharyngitis (1 subject, 1.4%). Dizziness and headache was only reported for subjects pretreated with DE who received idarucizumab doses below 5 g and not after infusion of placebo.

Frequencies of AEs during the post-treatment period were slightly lower for idarucizumab treated subjects (13.4%) than for placebo-treated subjects (16.2%). When comparing only subjects pretreated with DE, the proportions of subjects with AEs were nearly identical in the DE+Ida (11.1%) and DE+placebo (11.4%) groups. Subjects receiving only placebo had higher frequencies of AEs in the post-treatment period than subjects receiving only idarucizumab without DE pretreatment. For the post-treatment period, when taking into account only subjects who had been randomised to DE pretreatment, the AE frequencies were nearly identical in placebo-treated subjects and in idarucizumab-treated subjects who had received idarucizumab doses of ≥5 g,. The AE frequencies were slightly lower in the dose group who had been treated with <2.5 g idarucizumab and slightly higher in the 2.5 g to <5 g dose group. During the post-treatment period, the most frequent AEs for subjects in the Ida/DE+Ida group were nasopharyngitis (7 subjects, 3.1%) and influenza like illness (5 subjects, 2.2%), followed by headache, myalgia (each 3 subjects, 1.3%), and back pain (2 subjects, 0.9%). All other AEs were reported by less than 1% in the Ida/DE+Ida group (at most 2 subjects on preferred term level). The most common AEs for subjects in the placebo/DE+placebo group were very similar and included nasopharyngitis (4 subjects, 3.8%), influenza like illness, headache, and upper abdominal pain (each 2 subjects, 1.9%).

Regarding skin irritation, AE frequencies were slightly higher in the Ida/DE+Ida group (2.7%) than in the placebo/DE+placebo (1.9%) or the DE pretreatment (1.4%) groups, however, subjects treated with placebo alone had the highest frequency of skin irritation (5.7%). In study 1321.1, skin reactions were observed for 2 of 39 subjects on placebo placebo/DE+placebo) and for 4 of 118 subjects on idarucizumab (Ida/DE+Ida). Of the 2 placebo-treated subjects with AEs, 1 subject reported pain and 1 subject had swelling at the infusion site. Of the 4 subjects on idarucizumab who had AEs related to local tolerability, 1 subject reported swelling at the infusion site (after partial paravenous infusion), 1 subject had redness and pain, 1 subject was documented with heat and redness and 1 subject was reported with redness at the infusion site. In total, 2 subjects received the idarucizumab infusion partly paravenously: the subject with 200 mg idarucizumab infused for 1 h was not reported with any AEs related to local tolerability and 1 subject receiving the highest dose of 8 g idarucizumab (infused over 1 h) had swelling at the infusion site as stated above. All cases of skin reactions were of mild intensity and the subjects recovered without sequel. In study 3121.2, local tolerability of the study medication was good: 1 of 46 treated subjects reported swelling at the infusion site after infusion of placebo. In study 3121.5, no clinically relevant abnormal finding and consequently no AEs related to local tolerability of the infusion were recorded.

AEs related to bleeding were of special interest. Epistaxis occurred with higher frequencies in the DE pretreatment (2.1%) and placebo/DE+placebo (1.9%) groups than in the Ida/DE+Ida group (0.4%). Other AEs related to bleeding like gingival bleeding, ecchymosis, and infusion site haematoma were documented only for 1 subject each in the DE+placebo group (1.4%) and for none of the idarucizumab-treated subjects. Injection site haematoma was reported with nearly identical frequencies in the placebo/DE+placebo (1.0%) and Ida/DE+Ida (0.9%) groups.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

The investigators defined AEs in 5 patients as possibly drug-related (4 in Group A and 1 in Group B). These 5 patients had thrombotic events of which only 1 was within 2 days of idarucizumab treatment while the other 4 events occurred 7 or more days after treatment. Review of these 5 patients also revealed that only 1 of these patients had started antithrombotic medication.

8.3.2.2. Other studies

Possibly drug-related AEs according to the investigator were documented twice as frequent in placebo-treated subjects (placebo/DE+placebo: 6.7%) than in idarucizumab-treated subjects (Ida/DE+Ida: 3.1%). When considering only subjects who did not receive pretreatment with DE, subjects on placebo (placebo alone: 8.6%) were also more frequently reported with possibly drug-related AEs than idarucizumab-treated subjects (Ida alone: 2.8%). This pattern was consistent when comparing subjects pretreated with DE (DE+placebo: 5.7%, DE+Ida: 3.4%). Possibly drug-related AEs according to the investigator were documented in very few subjects on idarucizumab or placebo. In idarucizumab-treated subjects, the proportions of subjects with drug-related AEs in the dose categories up to 5 g were below or identical to those in placebo-treated subjects. Of the 9 subjects treated with idarucizumab doses of >5 g to ≤8 g, one subject (11.1%) was documented with possibly drug-related AEs (migraine) in the opinion of the investigator. Drug-related AEs as assessed by the investigator were reported with higher frequencies for placebo-treated subjects (placebo/DE+placebo: 6.7%) than for idarucizumab-treated subjects (Ida/DE+Ida: 3.1%), Overall, frequencies of possibly drug-related AEs in all idarucizumab-treated subjects were also lower than during DE pretreatment (4.3%). The most frequent AE on idarucizumab was epistaxis which was reported by 2[10] of 224 subjects (0.9%). On preferred term level, all other AEs were reported by at most 1 of 224 subjects (0.4%) after infusion of idarucizumab and comprised discoloured faeces, erythema, feeling hot, headache, infusion site erythema, migraine, and injection site haematoma. After infusion of placebo (placebo/DE+placebo), each type of possibly drug-related AE was reported by at most 1 of 105 subjects (1.0%) on preferred term level. These AEs included injection site haematoma, chest pain, ecchymosis, gingival bleeding, increased blood creatine phosphokinase, infusion-related reaction, infusion site haematoma, pain in extremity, and upper abdominal pain. During pretreatment with DE, 3 of 141 subjects (2.1%) were reported with the possibly drug-related events epistaxis and haematuria. Possibly drug-related AEs during the post-treatment period were documented for 1 subject (2.9%) in the placebo alone group and for 1 subject in the DE+idarucizumab group (0.9%).[11]

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

There were 26 deaths in the 123 patients included in this analysis, 13 in Group A and 13 in Group B. Thirteen of the deaths occurred in the first 5 days of the study, 6 in Group A and 7 in Group B, while the remaining 13 deaths occurred 6 or more days after treatment, with 7 in

[10] Specifically, 1 subject had epistaxis starting 2 days after infusion of 5 g+2.5 g idarucizumab in trial 1321.1 (Part 3); the event had a duration of 2 min . Another subject was reported with epistaxis (duration: 1 min) 7 days after infusion of 5 g idarucizumab in trial 1321.2.

[11] The idarucizumab-treated subject had epistaxis (7 days after last intake of study medication) and had been treated with 5 g idarucizumab in the mild renal impairment group of trial 1321.2. The event was of mild intensity, lasted 10 min, and the subject recovered without the need of additional medication. The placebo-treated subject had upper abdominal pain (6 days after intake of study medication) and participated in Part 1 of study 1321.1. The event was of mild intensity and lasted approximately 1.5 days; the subject recovered without concomitant therapy.

Group A and 6 in group B. The early deaths appeared to be progressions of the index events or underlying pre-treatment conditions. Eleven of the deaths occurred within 1 day of treatment, with 2 more deaths occurring before day 5. These early fatal events include shock with or without sepsis, peritonitis, cardiogenic shock, circulatory collapse, progression of intracranial bleeds, multiorgan failure, cardiac arrest, ruptured aortic aneurysm and respiratory failure.

The deaths after day 5 also included some patients with progression of the index event, such as bleeding, but also included deaths that were associated with co-morbidities (e.g. malignancies, Parkinson's disease, congestive heart failure).

Eight of the 26 deaths included bleeding (circulatory collapse, shock, gastrointestinal haemorrhage (N=2), ICH progression (N=3), haemorrhagic anaemia). The only death associated with a thrombotic event was an ischemic stroke (cerebral infarction) but this event occurred 26 days after treatment with idarucizumab and the patient was not receiving antithrombotic therapy at the time of the event. Mortality rate of intracranial haemorrhage patients is expected to be high and patients in Group A presented with ICH as the qualifying event with 6 of these cases being fatal (mortality rate of 25%). In comparison there were 27 GI bleeds in Group A and 3 of these patients died (mortality rate of 11.1%.).

Of 53 patients with SAEs, 24 were fatal AEs discussed in a previous section (plus 2 deaths categorised as screening events and not counted in the 53 post-treatment SAEs) and 5 were categorised as thrombotic and were discussed in section above. The remaining SAEs showed no consistent pattern apart from some association with the index events which led to their treatment in the study.

8.3.3.2. Other studies

In the combined Phase 1 studies, there were no deaths, no severe AEs and no SAEs during the treatment period.

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

No AEs led to discontinuation of study drug

8.3.4.2. Other studies

In the combined Phase I studies, there were no subjects with AEs leading to discontinuation of study drug.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

There were 3 patients with elevated transaminases and bilirubin who potentially met the laboratory criteria for Hy's Law cases, both before and after treatment with idarucizumab. Patient 3200105 had cholelithiasis and was to undergo urgent cholecystectomy. In all of these patients the elevations of the liver function tests could be attributed to the underlying conditions.[12]

8.4.1.2. Other studies

In the pooled Phase I studies, none of the subjects was reported with elevations of ALT and/or AST or total bilirubin >2x ULN at any time during the clinical studies. Similar frequencies of

[12] Patient [information redacted] was in renal and hepatic failure and required placement of a renal dialysis catheter. Patient [information redacted] had sepsis and was in renal failure; she required placement of a deep vein catheter, an arterial line and a dialysis catheter.

subjects on idarucizumab and placebo had elevations in ALT and/or AST >1x ULN. No clinically relevant difference in liver parameter elevations was observed when comparing subjects with and without DE pre-treatment. None of the subjects qualified for potential Hy's law. Subjects outside the normal range had maximum values of<2x ULN for both ALT/AST and for bilirubin.

8.4.2. Kidney function

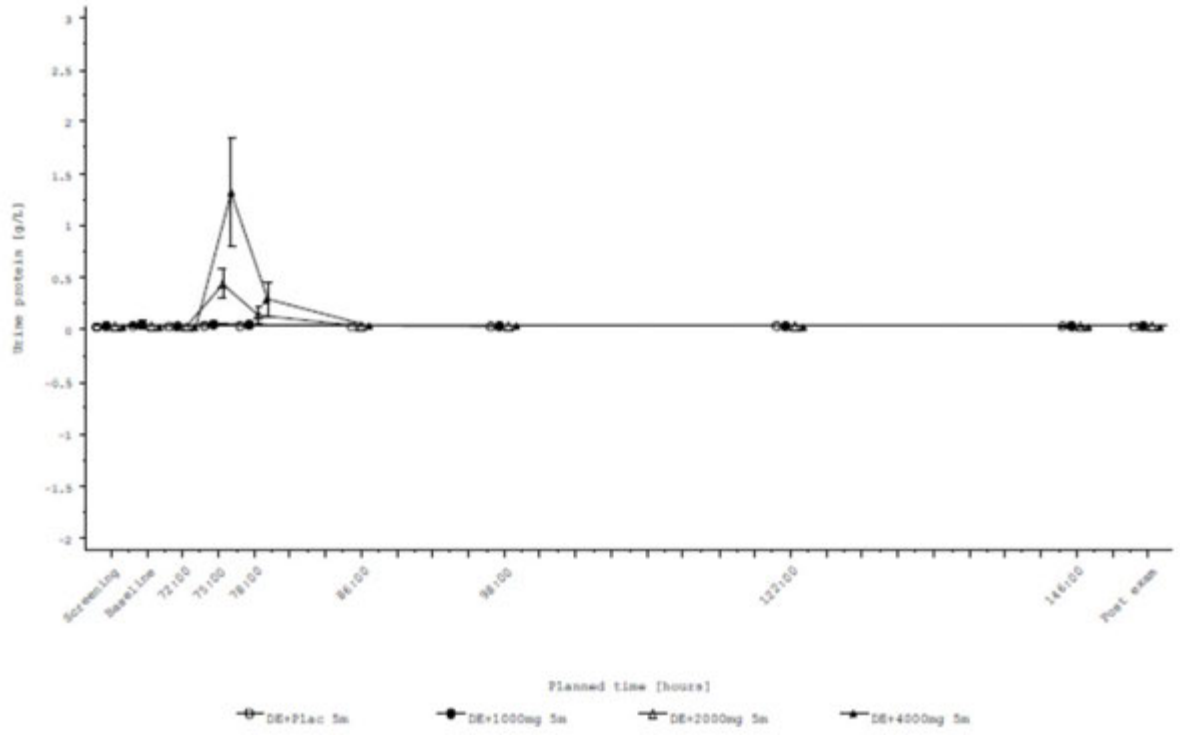
8.4.2.1. Pivotal studies

Abnormal values for serum creatinine were observed consistently although this was not unexpected, given the high rate of renal dysfunction. However, there was no detectable effect of idarucizumab on serum creatinine.

8.4.2.2. Other studies

For the parameters urine protein, urine albumin, urine IgG, and alpha-1-microglobulin in the urine, a dose-dependent increase was observed for all subjects at the time point 4 h after (first) infusion of idarucizumab which returned to normal reference range at the subsequent sampling time point, i.e. 4 to 12 h (studies 1321.1 and 1321.5) or 24 h (study 1321.2) after the (first) infusion of idarucizumab. As a representative example, the time course for urine protein is depicted in Figure 4 for subjects participating in Part 2 of trial 1321.1 who received a 5 min infusion of placebo or idarucizumab (1 g, 2 g, or 4 g). As observed in study 1321.2 which included subjects with renal impairment, the peak concentration of the urine parameters also depended on the renal function: good renal function of the subjects translated into lower peak concentrations than for subjects with lower renal function. For elderly subjects in the 1 g idarucizumab group, the peak of urine albumin and urine IgG concentrations was observed at the time point 24 h after infusion of idarucizumab; values returned to normal reference range at the subsequent sampling time point, i.e. 72 h after the infusion of idarucizumab. For all subjects in the individual Phase I trials, there were no corresponding urine changes such as increased glucose levels which would indicate acute tubular injury or loss of function.

Figure 4. Arithmetic mean of urine protein versus time (including SD) for subjects of Part 2 in Study 1321.1.



8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

While there were some patients with laboratory tests elevated or decreased outside the normal range, these were completely consistent with the patient population entered into the study. The most consistently abnormal values were for activated partial thromboplastin time (aPTT) and serum creatinine.

8.4.3.2. Other studies

No other significant changes in clinical chemistry parameters were observed in the Phase 1 studies.

8.4.4. Haematology

8.4.4.1. Pivotal studies

The abnormal values in haematology parameters observed in study 1321.3 were consistent with the proposed indication of severe bleeding or surgery in patients being treated with dabigatran.

8.4.4.2. Other studies

There were no significant changes in haematology parameters in the three Phase 1 studies in healthy volunteers.

8.4.5. Electrocardiograph

8.4.5.1. Pivotal studies

Changes in ECG were as expected in the target patient population with high comorbidity (95% of patients were taking dabigatran due to atrial fibrillation).

8.4.5.2. Other studies

In all three Phase 1 studies, a standard 12-lead ECG was conducted at the screening visit and throughout the study at each clinic visit until the End-of-Study Visit (at several time points). In addition, subjects in study 1321.1 underwent continuous ECG monitoring for 4 h starting immediately after the end of the infusion of idarucizumab. In all 3 Phase I studies, no clinically relevant abnormal finding and consequently no AE related to ECG data were reported.

8.4.6. Vital signs

8.4.6.1. Pivotal studies

Changes in vital signs were within expected ranges for the patient population studied with many unstable at entry and this was reflected by fluctuating vital signs.

8.4.6.2. Other studies

In each individual Phase I trial, vital signs were measured from the screening visit throughout the study at each clinic visit until the end-of-study visit (at several time points) with the subject rested for at least 5 min. At baseline, mean values for pulse rate as well as systolic and diastolic blood pressure were comparable between the treatment groups. Mean changes from baseline at any time point during the course of the studies were small and also similar across the treatment groups.

8.4.7. Specific safety parameter: administration of second dose of idarucizumab within 24 h of the first dose

There were two patients who entered the study after the 01 April 2015 cutoff that were not included in the analysis of 123 patients but deserve mention because they both received a second dose of 5 g idarucizumab due to re-bleeding.

These two cases are not yet completely reported to the database but they both indicate that there are patients where a second 5 g dose of idarucizumab may be effective in stopping bleeding. The high values of clotting tests at baseline in these patients suggest they have high body loads of dabigatran which may require more than 5 g for complete reversal. In these two cases, bleeding abated and clotting times improved after the first dose but bleeding re-started again later, in concert with elevated clotting tests. We evaluated the potential safety margin for a 10 g dose or 2 x 5 g 24 hours apart. Idarucizumab plasma levels and exposure in preclinical studies support administration of 5 g to 10 g to humans. Compared to healthy volunteers aged 45 - 64 years that received a 5 gram dose of idarucizumab, maximum plasma and exposure levels of 7-fold and 3 to 5-fold were reached in preclinical species at the No Observed Adverse Effect Level (NOAEL), based on mean Cmax and AUC0-24 levels of 25,000 nM and 37,000 nM·h reached in clinical trial 1321.2. These multiples remain unchanged if 10 g idarucizumab is administered as an initial 5 g dose followed by an additional 5 g dose greater than 24 hours later, as this regimen reflects the daily idarucizumab administration received by rats and monkeys in preclinical studies of 4- and 2-weeks duration, respectively. If idarucizumab is administered as a 10 g dose, multiples of exposure in preclinical species at the NOAEL decrease to 3-fold and 1 to 2-fold maximum plasma and exposure levels, respectively, based on estimated (modelled) human Cmax and AUC0-24 levels of 60,361 nM and 85,263 nM·h. In the event of impaired creatinine clearance (i.e., CrCL = 40 mL/min), the multiple between human maximum plasma levels and those in preclinical species decreases to 2-fold, with no effect on multiples of total exposure.

Comment: Preliminary results from these two patients suggests that a second dose of idarucizumab may be justified in case of re-bleeding in some patients.

8.5. Safety issues with the potential for major regulatory impact

8.5.1. Liver toxicity

None.

8.5.2. Haematological toxicity

None.

8.5.3. Serious skin reactions

No serious skin reactions were reported in the clinical studies.

8.5.4. Cardiovascular safety

None.

8.5.5. Unwanted immunological events

Overall, 18 of 224 subjects (8.0%) treated with idarucizumab in the Phase I studies had treatment emergent anti idarucizumab antibody responses. Responses were characterised as weak (that is, low titre, maximum titre = 40) and mostly non-blocking, with an even distribution between transient and possibly persistent responses suggesting that idarucizumab may have a low immunogenic potential.

In studies 1321.1, 1321.2, and 1321.5, pre-existing antibodies with cross-reactivity to idarucizumab were seen in 6.5% to 17.5% of subjects (overall 36/283, 13%). These were generally shown to be non-specific antibodies, with low titres, binding to the C-terminus of the molecule.

The presence of pre-existing anti idarucizumab antibodies did not impact reversal of dabigatran induced prolongation of clotting time for the parameters dTT and ECT.

To assess the potential impact of the anti idarucizumab antibody responses on the efficacy of idarucizumab in a subject who might require another course of idarucizumab treatment, a rough estimation of the amount of anti idarucizumab antibody in circulation and this was compared with the dose of idarucizumab that would be administered. For a titre of 40 (corresponding to roughly 3.3 µg/ml anti-drug antibodies [ADA]) and 3000 mL plasma volume of a 70 kg person, the amount of anti idarucizumab antibody in circulation calculates to be roughly 10 mg. For the proposed 5 g therapeutic dose of idarucizumab (resulting in peaks of ~20,000 nmol/L), it is clear that the dose is overwhelming in comparison to the estimated maximum concentration of treatment emergent anti idarucizumab antibodies observed to date. Therefore, it is concluded that the impact of anti idarucizumab antibody responses on the efficacy of idarucizumab should be minimal in subjects who may require additional courses of treatment.

In all 3 Phase I studies, antibody formation against idarucizumab and dabigatran was analysed throughout the study including a 3 month follow-up period. An antibody response was defined as treatment emergent in 2 cases. Either the subject showed no positive titre at baseline or a positive titre at post treatment visits. Alternatively, the subject had a positive titre at baseline and the titre increased at post treatment visits relative to the titres determined at earlier time points. No apparent correlation of antibody development to frequency of AEs was observed in any of the 3 Phase I studies.

In the Phase III Study 1321.3, data for ADAs against idarucizumab are available for 47 patients with a pre-dose sample and at least one post dose sample. There were 2 patients with baseline, non-specific ADAs, both of whom had persisting ADAs at 30 days but the binding is not at the variable site. One more patient had a treatment emergent ADA at 30 days, possibly of mixed specificity. These data are very limited but indicate a low level of immunogenicity for idarucizumab, consistent with the levels of immunogenicity identified in the healthy volunteer population from Phase I.

8.6. Post marketing data

Post marketing data are not available for idarucizumab as idarucizumab is not yet marketed.

8.7. Evaluator's conclusions on safety

In the three Phase I studies in volunteers, 283 subjects were studied, with 224 receiving at least one dose of idarucizumab. Dosing ranged between 20 mg and 8 g. Most of the doses were at least 1 g, with only 23 subjects receiving less than 1 g. Sixty-two subjects received doses of 5 g or more, with 35 subjects receiving the target clinical dose of 5 g. There were no SAEs in idarucizumab treated subjects, no discontinuations due to AEs, no severe AEs, and, importantly, no dose related AEs or drug reactions. There were no AEs associated with idarucizumab more than with placebo or other comparison groups such as treatment with DE alone. The most common events in subjects treated with idarucizumab were headache (5.4%), skin irritation (2.7%), dizziness (2.2%) and back pain (1.8%). The AE profile in volunteers did not suggest any worsening renal function. Overall, 18 of 224 subjects (8.0%) treated with idarucizumab in the Phase I studies had treatment emergent anti-idarucizumab antibody responses. Responses were characterised as weak (that is, low titre, maximum titre = 40) and mostly non blocking, with an even distribution between transient and possibly persistent responses suggesting that idarucizumab may have a low immunogenic potential.

Interim analysis from the ongoing idarucizumab Study 1321.3 (RE-VERSE AD), provided safety data for 123 patients There were 26 deaths in the study, 13 each in bleeding and surgical patients, reflecting the life threatening nature of the events that qualified them for treatment.. There were 5 patients with thrombotic events during the study but only one of these occurred

within 72 h of treatment and none of the patients were on antithrombotic therapy at the time of the event. One of these patients had an ischemic stroke 24 days after treatment and died 2 days later. The other SAEs in the study did not appear to be related to treatment.

The low immunogenicity of idarucizumab observed in Phase I subjects was confirmed in this interim analysis, although the subset was small (data on ADAs to idarucizumab was only available for 47 patients). There were no clear signals of any hypersensitivity reaction.

Overall, the safety in this open label patient cohort was good especially considering the severity of target patient population: (severe bleeding/need for surgery/ invasive procedure). However, interpretation was limited by lack of comparator group.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of Praxbind in the proposed usage are:

- Idarucizumab is a humanised monoclonal Fab that binds to dabigatran with very high affinity, approximately 300 fold more potent than the binding affinity of dabigatran for thrombin. The idarucizumab dabigatran complex is characterised by a rapid on-rate and extremely slow off-rate resulting in a very stable complex.
- Complete and sustained reversal of dabigatran induced clotting time prolongation was observed immediately after the idarucizumab infusion, lasting over the entire observation period of at least 24 h.
- Idarucizumab is specific reversal agent for only dabigatran and does not reverse effects of other anticoagulants.
- Idarucizumab has no prothrombotic effect.
- The reversal of the anticoagulant effects of dabigatran by idarucizumab has been demonstrated in 283 healthy volunteers (in 3 Phase I studies). Supportive evidence was provided by interim results from an ongoing Phase III, open label, uncontrolled, case cohort study in 123 patients, with uncontrolled or life threatening bleeding or those requiring emergency surgery/procedures when rapid reversal is required.
- No major safety concerns in a target population of elderly patients with a high frequency of co-morbidities who present at the hospital with a severe or life threatening bleed or a need for emergency surgery/intervention.

9.2. First round assessment of risks

The risks of Praxbind in the proposed usage are:

- Risk of thromboembolic events
- Hypersensitivity
- Immunogenicity
- Lack of data on clinical outcomes although it is accepted that it would be difficult to conduct controlled clinical trials in this target population.

9.3. First round assessment of benefit-risk balance

A small fraction of patients who are treated with DE and who have co-morbidities may require emergency surgery or other invasive procedures related to those co-morbidities, for example, cardiac catheterisation for a patient with acute coronary syndrome, surgery for a patient with acute appendicitis or major trauma without overt bleeding on presentation. Currently, there is no antidote available to reverse the anticoagulant effect of DE and the acute management of serious bleeding in patients on dabigatran etexilate, including life-threatening bleeds, is limited to supportive care, administration of blood or blood products and, in suitable patients, consideration of haemodialysis to remove the drug.[13] Similarly, there are no other alternatives for the management of dabigatran associated peri-operative bleeds.

Idarucizumab directly, rapidly and specifically neutralises dabigatran's anticoagulant effect due to its very high affinity for dabigatran (Kd = 2.1pM). This affinity is approximately 300-fold higher than the affinity of dabigatran for thrombin (Kd = 0.7 nM). This high affinity for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab. In dynamic equilibrium, any thrombin-bound dabigatran (or other plasma protein bound dabigatran) will equilibrate with unbound dabigatran and rapidly thereafter be bound by any free idarucizumab. Idarucizumab itself has no known pharmacologic effect and preclinical data have shown that it does not bind to factors in the coagulation cascade or other antithrombotics.

The reversal of the anticoagulant effects of dabigatran by idarucizumab, was demonstrated in volunteers, and the effect of the antidote in patients with uncontrolled or life-threatening bleeding or those requiring emergency surgery/procedures when rapid reversal is required is being evaluated in an ongoing study (1321.3) with interim data in 123 patients available at time of submission of current dossier. This was established using several different coagulation tests and corroborated by simultaneously measuring the disappearance of unbound sum dabigatran. An immediate, complete and sustained effect was demonstrated in healthy volunteers, in the elderly, in the renally impaired and in patients with life threatening or urgent conditions that required immediate intervention. This reversal was also demonstrated to be dose dependent and dependent on the amount of dabigatran in the patient. A dose of 5 g of idarucizumab was calculated to be sufficient for full reversal of dabigatran anticoagulant effect in 99% of patients, based on dabigatran plasma concentrations observed in the RE-LY trial. A massive amount of dabigatran, as could occur in cases of Pradaxa overdosage, may also be reversed by the proposed clinical dose of 5 g. However, plasma concentrations in excess of e.g.800 ng/mL may result in partial reversal. The complete dose of 5 g is administered intravenously, as two consecutive infusions over 5 to 10 minutes each or as a bolus injection. Local coagulation tests, for example, aPTT, dTT, pre and post treatment, may help the treating physician determine whether reversal of dabigatran has occurred.

The reversal of elevated anticoagulation tests in dabigatran treated patients is a surrogate for clinical efficacy. Together with a direct assay demonstrating the removal of "active" dabigatran (unbound sum dabigatran) from the plasma, these data document the pharmacologic effect of idarucizumab in the target population.

While improved clinical outcomes of, for example, reduction or stoppage of bleeding, or decrease in bleeding-associated mortality in a controlled clinical trial would be preferred, ethical and logistic constraints, as well as the need for an extremely large sample size, mean such a trial would take years to complete if it could be done at all. Even after over 50 years of use of warfarin and congeners, there are no clinical outcomes data showing clinical benefit or mortality reduction in bleeding patients on warfarin with administration of Vitamin K or fresh frozen plasma (FFP). In this context, demonstration of pharmacologic reversal of dabigatran in

[13] Weitz JI, et al. Periprocedural management and approach to bleeding in patients taking dabigatran. Circulation 126: 2428-32 (2012). Majeed A, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation* 128: 2325-32 (2013).

the target patient population, coupled with data in the same patients showing that unbound sum dabigatran levels were reduced at the same time was the proposed clinical development approach for idarucizumab.

The reversal of coagulation test values and reduced levels of unbound sum dabigatran reliably demonstrate reversal of dabigatran induced anticoagulation. Idarucizumab addresses the potential clinical need for an agent to rapidly reverse the anticoagulant effects of dabigatran in case of emergency surgery or life threatening or uncontrolled bleeding associated with dabigatran.

Idarucizumab is not intended for use in patients with minor bleeding or other bleeding where standard supportive care is sufficient. It is expected that usage of this drug would be confined to emergency departments or other critical care facilities.

Idarucizumab had an excellent safety profile in healthy volunteers with no SAEs, no discontinuations due to AEs, no severe AEs, and no dose related AEs or drug reactions. Similarly, in the 123 patients (included in the interim analysis of Phase III study 1321.3), AEs were common but appeared to be unrelated to treatment. Nine of the 26 deaths were either due to the events at presentation or later in the trial due to co-morbidities. The mortality rate was not unexpected in a high risk population with life threatening events. Though two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. Thus, there was no indication of a pro-thrombotic effect, consistent with evaluations in volunteers and with the preclinical data. There was no evidence of worsening renal function when this drug is given to patients with renal impairment and full efficacy is maintained. Other blood products may be administered as required.

Overall, the ability to safely reverse the anticoagulant effect of dabigatran in patients who require rapid reversal could improve the surgical risk of patients requiring emergency surgery, improve the management of serious bleeding events and further increase the overall safety profile of anticoagulation therapy with dabigatran.

The benefit-risk balance of Praxbind, given the proposed usage, is favourable.

10. First round recommendation regarding authorisation

It is recommended that approval be granted for Praxbind (idarucizumab) for the proposed indication:

> *Praxbind is a specific reversal agent for dabigatran and is indicated in patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of the anticoagulant effects of dabigatran is required:*
>
> - *for emergency surgery/urgent procedures*
> - *in life-threatening or uncontrolled bleeding.*

However, approval is subject to the following:

- incorporation of suggested changes to the proposed PI
- continued approval for this indication may be contingent upon the results of the ongoing cohort case series study (1321.3) and results should be provided for evaluation on completion of this study.
- an adequate response to questions below.

11. Clinical questions

11.1. Pharmacokinetics

None.

11.2. Pharmacodynamics

None.

11.3. Efficacy

11.3.1. Question 1

A 4 month safety update summarises safety and efficacy data from this ongoing study and provides data in 123 patients. However, the cover letter, clinical overview and clinical summary of efficacy in the current submission only summarise data in 26 patients from Study 1321.3. Can the sponsor please provide clarification on why data from the 123 patients was not included in the summary of efficacy or overview especially considering fact that both FDA and EMA mention data from 123 patients in their approval statements and labelling?

11.3.2. Question 2

Table 2.1.1:2 of the Clinical summary of efficacy mentions dose groups as Part 1 and Part 2 (see below: shown as Table 6).

Table 6. Comparison of mean $AUEC_{above,2-12}$ ratio post-Ida/pre-Ida for the coagulation markers dTT, ECT, aPTT and TT.

	$AUEC_{above,2-12}$ [h] ratio Day 4/Day 3			
Dose group	dTT	ECT	aPTT	TT
Part 1 *(5 min idarucizumab infusion)*				
DE+plc	1.01	1.04	1.28	1.08
DE+1 g Ida	0.26	0.28	0.46	0.32
DE+2 g Ida	0.06	0.07	0.14	0.06
DE+4 g Ida	0.02	0.03	0.07	0.00
Part 2 *(5 min idarucizumab infusion)*				
DE+2 doses plc	1.02	1.22	1.68	1.11
DE+5 g+2.5 g Ida	0.01	0.02	0.03	0.00

Plc=placebo, Ida=idarucizumab, DE=dabigatran etexilate
Ratios of $AUEC_{above,2-12}$ were calculated based on the effect ratio (observed value divided by baseline value) whereby only the area under the effect curve above 1 was considered.

There is an error in this table as Part 1 did not involve administration of dabigatran and it should actually read Part 2 and Part 3. Can the sponsor provide clarification on this?

11.4. Safety

None.

12. Second round evaluation of clinical data

A summary of the Sponsor's response to the clinical questions in section 12 is provided followed by the Evaluator's comments on this response.

12.1. Efficacy

12.1.1. Question 1

A 4 month safety update summarises safety and efficacy data from this ongoing study and provides data in 123 patients. However, the cover letter, clinical overview and clinical summary of efficacy in the current submission only summarise data in 26 patients from Study 1321.3. Can the sponsor please provide clarification on why data from the 123 patients was not included in the summary of efficacy or overview especially considering fact that both FDA and EMA mention data from 123 patients in their approval statements and labelling?

12.1.1.1. Sponsor's response

Based on pre-submission meeting agreements with FDA and EMA as well as TGA, Health Canada and other health authorities, submission of the initial idarucizumab dossier was based on the Phase I trials covering 283 volunteers and a first interim analysis covering 26 patients of the ongoing Phase III trial RE-VERSE AD (Trial 1321.3). Due to US regulation, an additional interim analysis (4-Month Safety Update) was performed for the US, which included up to 123 patients and covers the data presented in the June 2015 NEJM publication. The 4-Month Safety Update was submitted to FDA to fulfil the local regulatory requirement, to EMA as part of the responses to the Day 120 List of Questions and to other health authorities as applicable without concomitant update of the initial Module 2 documents. However, in the Summary and Conclusions section, the 4-Month Safety Update references the initial Clinical Overview and states the data and conclusions are consistent with the results of the initial interim report based on 26 patients.

12.1.1.2. Evaluator's comments

The Sponsor's response is satisfactory.

12.1.2. Question 2

Table 2.1.1:2 of the Clinical summary of efficacy mentions dose groups as Part 1 and Part 2 (see below: shown as Table 6).

There is an error in this table as Part 1 did not involve administration of dabigatran and it should actually read Part 2 and Part 3. Can the sponsor provide clarification on this?

12.1.2.1. Sponsor's response

The sponsors have acknowledged the typographical error in Module 2.7.3 Summary of clinical efficacy (Table 2.1.1.2) and mention that the trial parts are referenced correctly and the typographical error does not impact data or conclusions. Furthermore, a table with identical content was also provided in Module 2.7.2 Summary of clinical pharmacology (Table 2.1.1:5) and in this table the study parts have been correctly assigned.

12.1.2.2. Evaluator's comments

The Sponsor's response is satisfactory.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Praxbind in the proposed usage are unchanged from those identified in the first round evaluation.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Praxbind in the proposed usage are unchanged from those identified in the first round evaluation.

13.3. Second round assessment of benefit-risk balance

After consideration of the responses to clinical questions, the benefit-risk balance of Praxbind in the proposed usage is unchanged from that identified in the first round evaluation.

14. Second round recommendation regarding authorisation

It is recommended that approval be granted for Praxbind (idarucizumab) for the proposed indication:

> *Praxbind is a specific reversal agent for dabigatran and is indicated in patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of the anticoagulant effects of dabigatran is required:*
>
> - *for emergency surgery/urgent procedures*
> - *in life-threatening or uncontrolled bleeding.*

Continued approval for this indication may be contingent upon the results of an ongoing cohort case series study.

15. Population PK analysis

15.1. Rationale

This evaluation reviews a population PK analysis of idarucizumab and its interaction with dabigatran and effect on the PK-PD of dabigatran on coagulation biomarkers in three Phase I studies. The report is entitled “Idarucizumab and dabigatran population pharmacokinetics and dabigatran exposure-response relationships in healthy subjects”. The report was evaluated to determine the validity of the analysis methods and results and their clinical implications.

15.2. Evaluation of analysis conducted

15.2.1. Analysis conducted

The analyses conducted included a population PK analysis to characterise the disposition of and interaction between idarucizumab and dabigatran and PK/PD analyses to characterise the effect of dabigatran on coagulation biomarkers in three Phase I studies, 1321.1, 1321.2 and 1321.5.

Analyses were conducted by the sponsor.

15.2.2. Evaluation of analysis conducted

Base and final population PK models were evaluated. Analyses were run using NONMEM v7.3, whereas v7.2 was used to generate the PK results provided by the sponsor.

The PK control files for the base and final PK models, respectively, were run after simplification of the variance-covariance matrix to estimate only the diagonal elements. The results were compared with the sponsor's PK output files. Parameter estimation was successfully performed using the iterative two stage method and the Expectation Maximization using Monte Carlo importance sampling. However, implementation of the Stochastic Approximation Expectation Method failed to run successfully. Nevertheless, PK parameter estimates using the methods implemented were consistent with those reported by the sponsor and were deemed sufficiently similar to validate the sponsor's results.

15.3. Results of PK/PD report evaluation

15.3.1. Evaluation of Analysis Plan

A detailed analysis plan containing references to specific methodologies was provided that included the following:

- a clear statement of the objectives,
- a description of the studies and data, including number of subjects and nature of PK/PD data,
- procedures for handling missing, outlying and censored data,
- a description of analysis software and estimation methods,
- a detailed description of the modelling rationale, approach and structural and variability models,
- a list of covariates, rationale for their consideration, covariate model parameterization and modelling approach,
- details of model selection criteria and evaluation methods, and
- a summary of the simulations to be performed.

The Analysis Plan met the requirements of the EMA guidelines.

15.3.2. Evaluation of PK/PD Report Summary

The Synopsis comprised a comprehensive summary of the PK/PD report, including context of the study, objectives, study design, data, PK and PK/PD modelling and simulation methods, discussion of key results and list of conclusions. The synopsis met the requirements of the EMA guidelines.

15.3.3. Evaluation of Introduction to PK/PD Report

The Introduction of the PK/PD report provided a summary of the pharmacology of idarucizumab and the purpose of the analysis in the context of the clinical development program. The proposed modelling approach was discussed. As such, the Introduction complied with the EMA guidelines.

15.3.4. Evaluation of Objectives of PK/PD Analyses

The purpose of the analysis was stated in the PK/PD report and the objectives were clearly specified in accordance with EMA guidelines.

The objectives were to support selection of a proposed effective dose of idarucizumab and its regimen by:

- Characterising the population PK of idarucizumab and its binding interaction with dabigatran at a typical subject level and the associated between subject variability.
- Determining the relationship of sum dabigatran concentration and coagulation markers (ecarin clotting time (ECT), diluted thrombin time (dTT), activated partial thromboplastin time (aPTT), and thrombin time (TT)) before and after idarucizumab dosing.
- Evaluating the impact of co-administration and of several key demographic characteristics (covariates) on the PK and PD of idarucizumab and dabigatran.
- Providing PK-PD simulations.

15.3.5. Evaluation of data used in PK analyses

Data and data handling methods were described in the PK/PD report. A detailed description of the data was contained in the analysis plan and could have been referenced in the PK/PD report.

15.3.5.1. Data included in the analyses

The population PK analysis included data from 3 intensively sampled phase 1 studies. Study designs were summarized.

- Study 1321.1 assessed safety, tolerability and PK of single doses of idarucizumab (part 1) and explored its PK/PD and effective dose range for single doses alone and after steady-state dabigatran etexilate (DE) in male healthy volunteers (HV),
- Study 1321.2 assessed safety, tolerability and PK/PD of single doses of idarucizumab after steady-state DE in male and female HV, elderly HV and volunteers with mild or moderate renal impairment,
- Study 1321.5 assessed safety, tolerability and PK of single doses of idarucizumab alone and after steady-state DE in male Japanese HV.

Idarucizumab was administered as a single dose (0.02-8 g) alone or 2 h after twice daily (BID) DE either as a single dose (1-5 g) or a series of two doses separated by 0.25 h or 1 h.

Analytes included in the PK and PK/PD analyses were as follows:

- Sum dabigatran – total concentration of bound and unbound dabigatran and dabigatran metabolites (glucuronide conjugates) in plasma. 'Bound' refers to plasma protein binding and binding to idarucizumab.
- Unbound sum dabigatran – free concentration of dabigatran and dabigatran glucuronides, i.e., not bound to plasma proteins or idarucizumab.
- Idarucizumab – total idarucizumab including free or bound to dabigatran or dabigatran metabolites.

In addition, the PK/PD analysis included the derived quantity, idarucizumab-free sum dabigatran (IFSD), defined as sum dabigatran not bound to idarucizumab.

PK/PD data sets were constructed by merging observed and individual PK model-predicted concentrations of unbound sum dabigatran and predicted IFSD with individual anticoagulation biomarker data (ECT, dTT, TT and aPTT).

Plasma and urine samples were collected. Plasma samples were assayed for dabigatran analytes, idarucizumab and coagulation tests. Sampling times were not specified, however, the duration of sampling and average number of PK and PD samples per subject were stated in the PK/PD report. Although not stated, analysis of urine PK was not included in the PK/PD report.

Subjects with at least one recorded post-dose PK sample or one anticoagulation biomarker measurement were included in the PK and PK/PD data sets, respectively.

A data specification file (define.pdf) was provided that listed the variables and definitions for each of the PK/PD analysis sets. A table of detailed field descriptions for the PK and PK/PD data sets was also included in the PK/PD report.

15.3.5.2. Procedures for handling missing data and outliers

Handling of missing samples was described. In accordance with the analysis plan, missing idarucizumab concentrations, dabigatran analyte concentrations and coagulation data were excluded from the analysis set. There were no missing dose times.

Samples from treated or placebo subjects that were below the limit of quantification (BLQ) for dabigatran analytes were included in the data set as "0" values and identified with a flag to allow evaluation of censored observations in the model development.

Procedures for handling of BLQ idarucizumab samples were not described in the analysis plan or the PK/PD report. The data specification file indicated that these samples were excluded from the analysis using the CMNTS (Comment) field. However, no justification was provided for their exclusion.

Handling of outliers for the PK analysis was described, as per the analysis plan. In section 8.3.2, sensitivity analyses were proposed to evaluate the impact of outliers on both PK and PK/PD results, although the sensitivity analysis was not initially planned for the PK/PD analyses. However, definition of outliers and methods for their identification were not stated.

15.3.5.3. Covariates

Baseline covariates included in the analysis dataset were age, weight, sex, race and creatinine clearance (CrCL). Derivation of CrCL using the Cockcroft-Gault equation was stated. Handling of missing covariates was not specified, however, it was stated in the analysis plan that there were no missing covariates across studies.

15.3.5.4. Data summary

Notwithstanding minor omissions (sample timing, identification of outliers), the Data section of the PK/PD report provided a clear overview of the studies and data handling methods. As a result the data description largely met the criteria of EMA guidelines.

15.3.6. Evaluation of methods used in the analyses

15.3.6.1. Bioanalytical methods

Bioanalytical reports for all analytes were provided in the m2 module document, 27-summary-biopharm.pdf, as referenced in the PK/PD report. Analytical methods, validation data, assay range and lower limits of quantitation (LLOQ) were provided for idarucizumab and dabigatran analytes. Bioanalytical assay details and validation data were also provided for each of the PD endpoints.

15.3.6.2. Choice of analysis and software

Model-based PK analyses were implemented using the nonlinear mixed effects modelling program, NONMEM (version 7.2). Population PK analyses were conducted initially using the First Order Conditional Estimation (FOCE) method with LAPLACIAN option (for implementation of M3 method). Newer estimation methods (Stochastic Approximation Expectation Method (SAEM), Iterative Two Stage method (ITS) and Expectation Maximization using Monte Carlo Importance Sampling (IMP)) were also implemented. The analysis plan specified that Monolix may also have been used for PK model development.

PK/PD analyses were performed using linear mixed effects (lme) and nonlinear mixed effects (nlme) regression functions in R version 3.0.3. In addition, model diagnostics and parameter tables were constructed in R.

The computing environment was not stated. However, the choice of analysis software was appropriate for the analyses conducted.

15.3.6.3. PK modelling methods

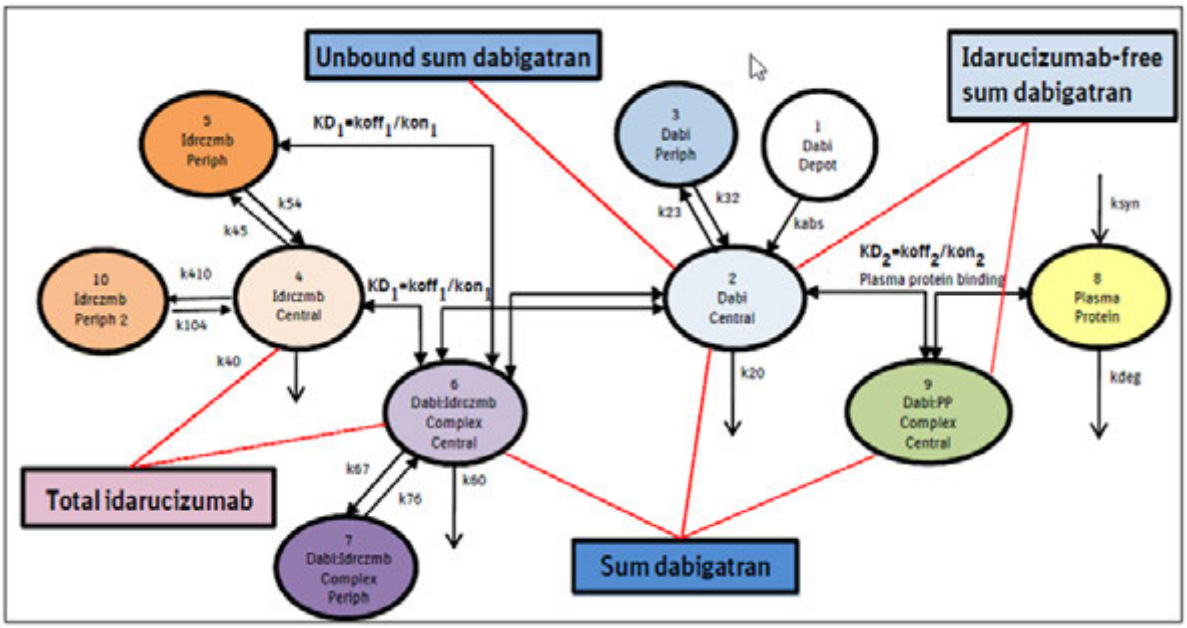
PK modelling methods were described in the PK/PD report. A more detailed description of the PK modelling methods was contained in the analysis plan and could have been referenced in the PK/PD report.

Structural model

PK model development was informed by previous preclinical PK analysis of dabigatran and idarucizumab and digoxin-Fab, as well as initial analyses of study 1321.1. Initially a two compartment model with first order absorption was used to describe dabigatran PK and a three compartment model was used to describe idarucizumab disposition.

A schematic of the PK model is shown in Figure 5. The measured analytes and their associated compartments were unbound sum dabigatran (CMT=2), sum dabigatran (CMT=10, sum of CMTs 2, 6 and 9) and idarucizumab (CMT=4). Simultaneous PK modelling of these analytes permitted characterization of a dabigatran species bound only to plasma proteins (CMT=9), which in turn allowed IFSD to be derived (sum of CMT 2 and 9). Figure 5 contained a typographical error: the peripheral idarucizumab designated CMT=10 should have been labelled CMT=11, since CMT=10 represented sum dabigatran. Similarly the differential equation for CMT=10 should have referenced CMT=11, consistent with the coding of the model in NONMEM.

Figure 5. Schematic representation of dabigatran and idarucizumab PK binding model depicting a two compartment PK model for dabigatran and idarucizumab and the dabigatran:idarucizumab complex.



Modelling assumptions specified appeared reasonable.

- Unbound sum dabigatran from the central compartment and unbound idarucizumab from central and peripheral compartments were available to bind and form the dabigatran-idarucizumab complex. The complex was assumed to arise from a second-order formation process and equimolar binding. Its volume of distribution and first order elimination were assumed to be that of unbound idarucizumab (V6 = V4 and k60 = k40).

- Experimentally determined values were initially used for dabigatran-idarucizumab binding rate constant, unbound sum dabigatran – plasma protein affinity constant and dissociation rate constant.
- Dabigatran absolute bioavailability was assumed to be 6.5% based on prior knowledge.
- Protein binding capacity was assumed to be constant over the time course of the study.
- After binding to idarucizumab, rapid equilibration of unbound plasma dabigatran (from tissue into plasma) occurred at a rate equal to k32 (not k21 as incorrectly stated in the PK/PD report).

Proposed model variations evaluating source of binding moiety (central compartment vs. central + peripheral compartments) and potential nonlinearities with dose and time were plausible and appropriate. Given that non-nested models were likely to be tested, use of the Akaike Information Criterion (AIC) for model selection might have been considered instead of the NONMEM objective function value (-2 x log likelihood).

The M3 method (Ahn et al., 2008) was used to incorporate into the model the effects of censored unbound sum dabigatran following idarucizumab administration and sum dabigatran concentrations during the elimination phase.

Parameter estimate confidence intervals for the final population PK model were estimated using the $COV option in NONMEM.

Variability models

Once the structural model was selected, block elements of the Ω matrix were evaluated using the condition number as a guide. Interindividual variability was assumed to be have a log-normal distribution. Standard residual error models (additive, proportional, additive in log domain) were tested for each of the three analytes in the PK analysis.

Covariate model

Covariate selection was based on prior knowledge or literature data, with priority given to established PK relationships (e.g. renal function and CL). On this basis, body weight on volume of the central compartment (Vc) and CrCL on clearance (CL) were tested for idarucizumab and CrCL and age were tested on dabigatran apparent clearance (CL/F). In addition potential drug interactions due to coadministration of dabigatran and idarucizumab were tested. The frequency and effect of anti-idarucizumab antibodies on idarucizumab exposures was not considered in the analysis.

Subsequently, race was tested on idarucizumab Vc and CL and dabigatran CL/F. Sex was also tested on idarucizumab CL.

Following univariate analysis of covariates in NONMEM, a forward addition/backward elimination process was used to build the population PK model. A decrease (for covariate additions) or increase (for covariate deletions) of 10 points in the NONMEM objective function value (OFV) was considered significant; the rationale for this approach was appropriately referenced (Wahlby et al. 2001) and acceptable.

The effects of continuous covariates were modelled using power models while categorical covariates were modelled using a factor term. An Emax model was used to describe the effect of CrCL on dabigatran CL/F in the RE-LY study (Liesenfeld et al., 2011), however, this model was not tested.

In a change in the conduct of the study relative to the specifications in the analysis plan (as outlined in the PK/PD report), the effect of Japanese race in the final PK/PD models was replaced with a study effect. The rationale for this change was that the effect of race could have originated from between study differences in bioanalytic procedures. The approach for handling this change appeared to be sound.

15.3.6.4. PK/PD modelling methods

PD modelling methods were described in the PK/PD and in the analysis plan. Relationships between coagulation markers and the independent variables, unbound sum dabigatran and IFSD, in the presence and absence of idarucizumab were modelled using linear and nonlinear (Emax) functions. Interindividual variability (IIV) was assumed to be normally distributed for correlated PK/PD parameters (full variance-covariance matrix). Residual error was modelled using an additive term, although proportional error models were also possible.

Effects of idarucizumab administration, age, body weight, sex and race were subsequently evaluated on the structural PK/PD parameters. The effects of continuous covariates were modelled as linear predictors while categorical covariates were modelled using a factor term. Following univariate covariate additions, a forward addition/backward elimination process was used to build the population PK/PD model. A decrease (for covariate additions) or increase (for covariate deletions) of 10 points in the Akaike Information Criterion (AIC) was considered significant; the approach was deemed acceptable.

15.3.6.5. Model evaluation

Model evaluation methods used to guide model development were stated in the PK/PD report.

For the PK model, standard diagnostic criteria were implemented, including successful minimization, precise parameter estimation, homoscedastic appearance of goodness of fit plots, acceptable shrinkage, and visual predictive checks (VPC) using 300 simulated replicates of the data sets. A focus of the evaluation of dabigatran VPC plots was to assess the adequacy of the binding model to describe the dabigatran-idarucizumab interaction. Parameter estimate confidence intervals using nonparametric bootstrap was not considered due to the long run time.

For the PK/PD model, goodness of fit plots were evaluated together with VPCs using 200 simulated replicates of the data set.

15.3.6.6. Simulations

Simulation methods were outlined in the PK/PD report. The purpose of the simulations was to explore the impact of renal function and idarucizumab dose on exposures to idarucizumab and dabigatran and anticoagulation responses to dabigatran. Fixed effects and random effects PK binding parameter estimates and fixed effects PD parameter estimates were used. It was noted that inclusion of IIV on the PD parameters did not alter the results, since the magnitude of IIV on PD parameters was small relative to that on the PK parameters.

Simulations were performed for typical subjects (40 y, 80 kg Caucasian males and 60 kg Japanese males) and typical patients (75 y, 80 kg Caucasian males and 60 kg Japanese males) with CrCL of 40, 60, 90 and 120 mL/min. The final PK binding model was used to simulate 300 IFSD profiles for each of the typical subjects and typical patients following steady-state administration of DE (BID dosing over 3 days and a single dose on Day 4) at a dose of 220 g for 40 y and 150 mg for 75 y subjects. Single idarucizumab doses of 1, 2 or 5 g or two doses of 2.5 g separated by 15 min were administered at the approximate time of the maximum steady-state dabigatran concentration on day 4. Sampling times were at most 30 min apart over the 4 h period after idarucizumab administration.

Simulations were also performed using the dabigatran CL/F vs. CrCL relationship ($CL = CL_{max} \times CrCL^{\gamma}/(EC_{50,CrCL}^{\gamma} + CrCL^{\gamma})$) previously established from the population PK analysis of the RE-LY study (Liesenfeld et al., 2011).

The PD measurement of interest was the reversal of dabigatran-induced anticoagulation after idarucizumab administration, calculated as follows:

$$\%\ \text{Reversal} = \frac{predose\ coagulation\ test - minimum\ postdose\ coagulation\ test}{predose\ coagulation\ test - 110\%\ ULN} * 100\%$$

where values of 110% ULN for ECT and dTT were provided in the PK/PD report.

The following anticoagulation responses were determined: % reversal both pre-and post-idarucizumab administration, maximum % reversal within 4 h after last idarucizumab administration and duration of reversal, defined as the time period a patient remained completely reversed based on dTT or ECT measurements up to twenty four hours post dose or upon re-starting treatment with dabigatran.

15.3.6.7. Methods summary

Overall, the Methods section of the PK/PD report provided a detailed, reasoned description of the PK and PK/PD model-building methods with appropriate choice of models and appropriate justification for assumptions implemented and methods used. Cross-referencing with the analysis plan would have further enhanced the readability of this section. Nevertheless, the Methods met the requirements of the EMA guidelines.

15.3.7. Evaluation of results

15.3.7.1. PK Data description

A review of the PK data set revealed that it contained 16059 records from 257 subjects. A total of 2395 observations (including 2122 BLQ idarucizumab observations, of which 685 were associated with placebo doses, and 188 BLQ pre-dose unbound sum dabigatran and sum dabigatran observations) and 4 dosing records were excluded from the analysis using the CMNTS field. After exclusion of these records, there were 13660 records from 244 subjects included in the PK analysis, as stated in the PK/PD report.

In the PK/PD report it was noted that complete records (including idarucizumab doses and PK profiles) for 4 subjects [information redacted] in study 1321.1 were excluded from the analysis as their profiles were not monotonically decreasing. An idarucizumab observation for subject [information redacted] was also excluded. Review of the PK analysis set revealed that this observation was a quantifiable idarucizumab concentration following placebo administration. The rationale for exclusion (using CMNTS = "C") of an additional 5 idarucizumab measurements (one sample from each of 5 subjects) and one unbound dabigatran BLQ observation in study 1321.2 was not stated in this section of the PK/PD report. These samples were labelled as "noisy" and were excluded as outliers, although the term "noisy" was not defined. Similarly, the rationale for ignoring BLQ idarucizumab observations was not stated. In addition:

- a complete description of the PK data set including a complete description or listing of the 2399 excluded observations and 13 excluded subjects using CMNTS = "C" to derive the PK analysis data set would have been desirable,
- a statement of the number of imputed doses in the data set would also have been desirable,
- the data description stated that it included only quantifiable concentrations, however, MDV=1 samples were included in the counts, and
- there were 18 (not 15) subjects in the analysis set who received 150 mg dose of dabigatran.

Descriptive statistics of the number of observations and doses by study and treatment group were presented in the PK/PD report. Scatter plots of unbound sum dabigatran, sum dabigatran and idarucizumab plasma concentrations vs. time after last dose by study and dose (and infusion duration for idarucizumab) for the PK analysis data set were also presented. Graphical presentation of outliers excluded from the PK analysis was not shown. A box plot showing the

distributions of peak sum dabigatran concentrations by study and dose compared to RE-LY study was shown.

15.3.7.2. PK/PD data description

Separate PK/PD data sets were constructed for analysis of observed and individual model-predicted unbound sum dabigatran/PD relationships and individual model-predicted IFSD/PD relationships. Since PK and PD samples were collected at the same times, merging of PK and PD data sets in R was straightforward. Although inconsequential, small negative values of model-predicted IFSD (<-$1e^{-7}$) could have been fixed to 0 on the basis of biological implausibility.

Subjects were required to have at least one coagulation biomarker measurement to be included in the PK/PD analysis set. A review of the PK/PD data sets revealed that they contained 4690 – 4692 records per coagulation biomarker from 189 subjects for the unbound sum dabigatran/PD data set and 4697 – 4699 records per coagulation biomarker from 189 subjects for the IFSD/PD data set. Based on review of the data sets, 176 subjects were included in both the PK analysis set and the PK/PD analysis set and 13 subjects were included in only the PK/PD analysis set with assigned observed and predicted dabigatran concentrations of 0. Subjects in studies 1321.1 and 1321.5 included in the PK analysis set but not the PK/PD analysis set were all assigned to receive single dose idarucizumab (without dabigatran dosing).

Descriptive statistics of the number of PK/PD observations by study were presented in tabular form in the PK/PD report and were consistent with values obtained from a review of the data sets. Distributions of dabigatran species and coagulation biomarkers by study were also tabulated. Plots showing the distributions of coagulation biomarkers during various phases of treatment were shown.

Correlations among dabigatran species and coagulation biomarkers were all highly correlated ($r > 0.8$). Model-predicted unbound sum dabigatran and IFSD were perfectly correlated ($r = 1$).

15.3.7.3. Base PK model

The PK model development process was described in the PK/PD report and corresponded with the listing of model development steps presented. The FOCE method failed to successfully converge and was rejected in favour of SAEM estimation followed by IMP estimation to obtain an alternative OFV used in model selection.

The PK model comprised a two compartment model for dabigatran and a three compartment model for idarucizumab with additive and proportional error terms for idarucizumab and the dabigatran moieties in the log domain. PK parameter estimates for dabigatran were of similar magnitude to previously published values, as referenced in the PK/PD report. Interpretation of the idarucizumab PK parameter estimates was appropriate. An additional compartment was employed to permit formation of idarucizumab-dabigatran complex from unbound sum dabigatran (central compartment only) and unbound idarucizumab (central and peripheral compartments). Estimation of an *in vivo* idarucizumab-dabigatran binding affinity constant (K_d) that was 130-fold higher than the experimentally-determined *in vitro* K_d value resulted in a decrease in OFV by 1043 points.

With respect to the model building table presented:

- The majority of models listed aimed to optimize random effects models with few structural perturbations. Some key models were omitted, e.g. effect of lag time on dabigatran absorption, evaluation of number of compartments for idarucizumab, diagonal variance elements vs. full variance-covariance matrix.
- Although proposed in the Methods, dose and time dependencies were not evaluated in the PK model development.
- The effect of outliers on parameter estimation was not assessed.

- Inclusion of the results of runs 1009 and 1023 would have been useful to review the impact of the M3 method on PK parameter estimation,
- In view of the large difference in estimated in vivo Kd (compared to the in vitro value), sensitivity analyses to test the values of binding parameters (i.e., Kon and Koff values) would have been useful to examine the validity of these assumptions and their impact on goodness of fit.
- Given variations in OFV values with different initial estimates, consideration might have been given to re-assessment of the choice of ΔOFV for covariate selection.
- Effects of age and CrCL on dabigatran CL/F, renal impairment on dabigatran CL/F and intercompartmental clearance (Q/F), CrCL on idarucizumab CL and body weight on idarucizumab Vc were included in the base model based on previous modelling experience. Contrary to the approach stated in the Methods, the statistical significance of these covariates was not tested. Indeed, the addition of age on dabigatran CL/F did not meet the inclusion criteria of > 10 point drop in OFV (model 1008 vs. model 2000 in showed a decrease of 6 points). Moreover, evaluation of these covariates as part of the covariate assessment after base model development would have been desirable in order to allow evaluation of the goodness of fit of the structural binding model in its simplest form.

Nevertheless, the form of the binding model was appropriate as shown by acceptable goodness of fit plots (Figure 6). Figure 6 showed good agreement between observed and both population (PRED) and individual (IPRED) predicted plasma concentrations of idarucizumab (CMT=4) and unbound sum dabigatran (CMT=2). For sum dabigatran (bottom row, left panel of Figure 6; see below), the smoothing function showed a trend towards underprediction of sum dabigatran concentrations > 1100 ng/mL. This bias was also evident in the residual vs PRED plots for sum dabigatran (shown below). While for unbound sum dabigatran, there was some bias in the residual vs time plots at very late times (~2000 h). Diagnostic plots of observations and model predictions in the log domain were not presented.

Figure 6. Observations vs PRED (left panel) and IPRED (right panel) for base model. Red solid line represents unity; red dashed line represents a smoothing function.

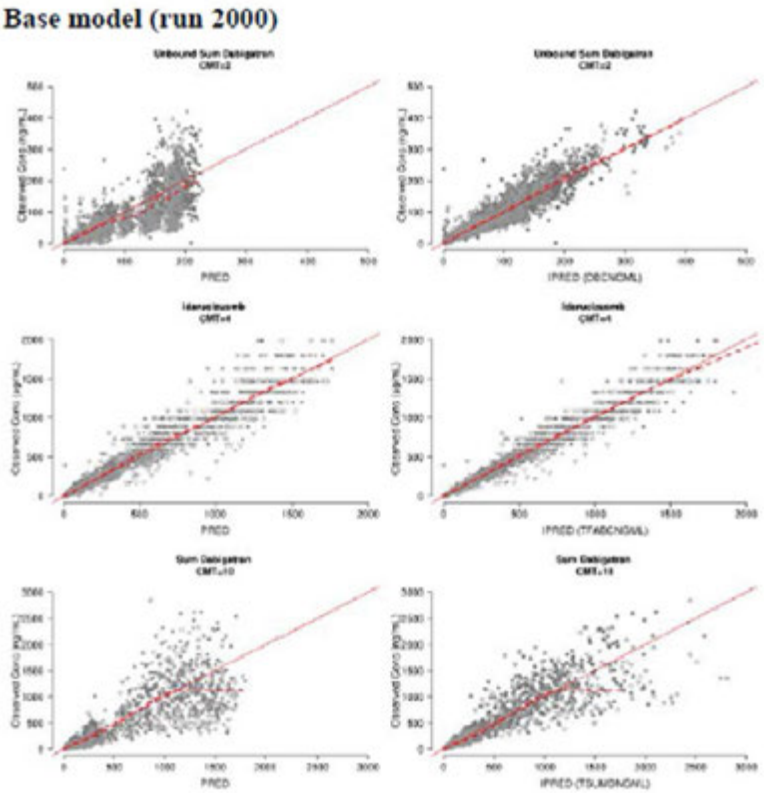


Figure 6. Individual weighted residuals (IWRES) vs PRED for base model. Red dashed line represents a smoothing function.

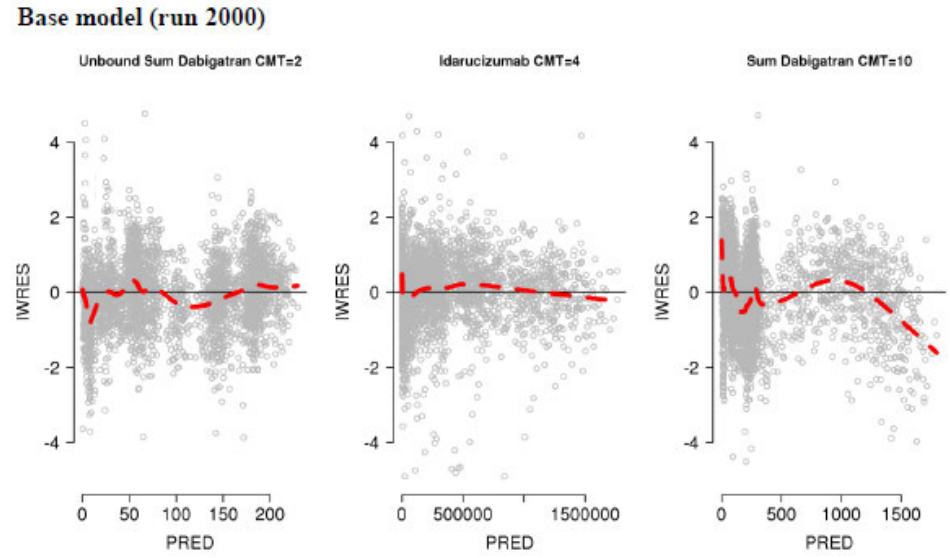
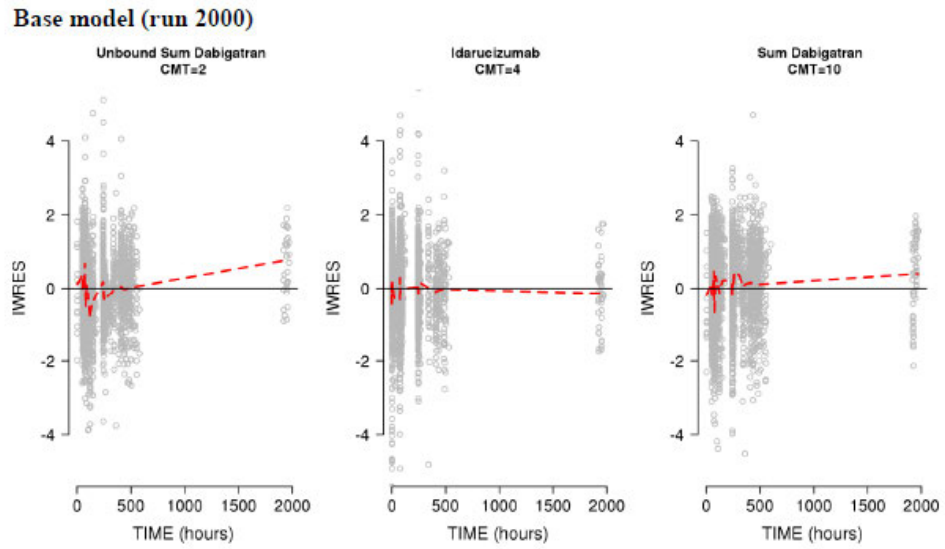


Figure 7. Individual weighted residuals (IWRES) vs time after first dose for base model. Red dashed line represents a smoothing function.



Structural PK parameters and residual random error terms were estimated with good precision.

Variance parameters were estimated with acceptable precision and good ETA shrinkage (<40%). Large IIV was estimated for idarucizumab peripheral volume (Vp) but with high precision. Off-diagonal elements should have been reported as covariances not correlations and were less precisely estimated compared with the variances. Assessment of a model with diagonal elements compared with the model with full covariance matrix would have been a useful addition to the model building table. Correlations among variance parameters were reasonable.

15.3.7.4. Final PK model

In the covariate analysis, sex and race were tested on idarucizumab CL and dabigatran CL/F. The run log did not include assessment of the effect of dabigatran exposure on idarucizumab PK. Race was determined to be significant on both PK parameters and retained in the final model. Based on the final model, dabigatran CL/F was estimated to be increased by 16% and idarucizumab CL was estimated to be reduced by 11% in Japanese subjects compared to Caucasian subjects. The OFV for the final model incorporating these effects of race in study 1321.5 was 77 points lower than that for the base model.

Final population PK parameter estimates were tabulated in section 10.1.4 of the PK/PD report and derived from model 2102, which was identified as the final model in the body of the PK/PD report. However, the model development table presented in the identified model 2300 as the final model and this was the model included and incorrectly cross-referenced as the source for parameter tables in the PK/PD report. Model 2300 differed from model 2102 only in the initial estimates for the race effects and resulted in similar parameter estimates and similar OFV (based on IMP estimation). Output for model 2102 was included with the analysis files and corresponded with the tabulated parameter estimates in the structural model, inter-individual random effects model, and residual random effects model.

PK parameter estimates, including structural and random effects parameters, for the final model were comparable to the base model. One exception was the effect of age on dabigatran CL/F which changed from an inverse relationship in the base model to a small direct relationship with negligible impact on dabigatran CL/F in the final model. Consequently, consideration should have been given to exclusion of this effect on the basis of clinical irrelevance.

As there was no observable difference in the goodness of fit as a result of including race on idarucizumab CL and on dabigatran CL/F, diagnostic plots for the final model remained unchanged relative to those for the base model. Therefore, the goodness of fit plots are not shown again here (refer instead to goodness of fit plots for base model in section 5.7.3 of this review). Of note, the trend towards underprediction of sum dabigatran concentrations > 1100 ng/mL was present in the observed vs. PRED/IPRED and IWRES vs. PRED plots for the final model as well as the base model. It was unfortunate that there was no commentary on possible reasons for this bias in the model.

Other diagnostic plots, including distributions of ETAs and ETA-covariate relationships, were reasonable and did not point to significant flaws in the model assumptions.

VPC plots were presented in the PK/PD report. These showed good performance of the model in capturing the central tendency and variability in the idarucizumab plasma concentration vs. time profiles by dosing cohort. The model also did an impressive job in capturing the shape of the redistribution phase for dabigatran moieties after idarucizumab administration and the frequency of BLQs. However, the VPC identified deficiencies in the model such as prediction of higher than observed plasma concentrations of the dabigatran moieties in the absence of idarucizumab in study 1321.1 and sometimes inconsistent performance in capturing the dabigatran redistribution phase after high dose idarucizumab administration. Alternative binding models incorporating time-dependent PK parameters were proposed to further explore model deficiencies going forward.

Notwithstanding the model deficiencies, the model evaluation showed that the model provided a reasonable description of the PK profiles for idarucizumab and dabigatran moieties following dabigatran-idarucizumab interaction. Application of the binding model to patient data remains to be evaluated, together with investigation of the covariate effects of interest including race, body weight, renal function and anti-drug antibodies on dabigatran-idarucizumab PK in patients.

15.3.7.5. PK/PD models

The PK/PD model development process for each of the coagulation biomarkers, ECT, dTT, aPTT and TT was described in the PK/PD report and corresponded with the listing of model development steps presented. Analyses were performed using lme and nlme functions in R. Results presented in the body of the report were for the independent variable, observed unbound sum dabigatran. Presentation of the results for IFSD as the independent variable in the body of the PK/PD report may have been more appropriate since IFSD-coagulation biomarker relationships were the primary relationships of interest that were used for simulations.

Two sets of analyses were performed. The first set of covariate evaluations included race as a covariate. The second set of evaluations replaced race effects in the final covariate models with study effects, as noted previously in this review.

As part of the PK/PD model evaluations, it was stated that sensitivity analyses were conducted to evaluate the impact of outliers on parameter estimates. Outliers were identified as samples with associated absolute standardized residuals > 10. These samples were tabulated for each PK/PD analysis. Results of the sensitivity analyses were reported as part of the model evaluation by coagulation biomarker. With the exception of the TT analyses for which parameter estimates with and without outliers were reported, none of the exclusions resulted in > 20% impact on parameter estimation.

The PK/PD modelling results showed consistency in parameter estimates for all three independent variables, observed unbound sum dabigatran, model-predicted unbound sum dabigatran and IFSD. Furthermore, the covariate assessment showed a lack of effect of idarucizumab on the slope of dabigatran's PK-coagulation biomarker responses.

ECT

The relationship between observed unbound sum dabigatran and ECT was described using a linear slope-intercept model with additive, correlated IIV terms on both intercept and slope and additive residual variability. There was a significant effect of Japanese race on the intercept compared to non-Japanese resulting in a 15% decrease in intercept IIV and a 48 point decrease in AIC. With the evaluation of study effects, the effect of Japanese race on intercept was exchanged with a corresponding effect of study 1351.5. In addition, intercept and slope were increased for study 1351.1. AIC for the final model was decreased by another 47 points and IIV was reduced for both slope and intercept relative to the model including race. All PK/PD parameters were estimated with good precision.

Similar results were obtained for the models using both model-predicted unbound sum dabigatran and IFSD as the independent variable. However, in both cases, the covariance matrix was nonpositive definite and bootstrap estimates of the 95% confidence intervals for parameter estimate were obtained. It would have been useful to see whether simplification of the variance-covariance model obviated this result for the unbound sum dabigatran and IFSD – ECT models.

Goodness of fit plots were presented. Although goodness of fit plots lacked trend lines, there appeared to be reasonable agreement between observed ECT and both PRED and IPRED ECT values. ETAs and residuals appeared uniformly distributed. Correlation between ETAs for the observed unbound sum dabigatran model was reasonable, while for the model-predicted moieties the correlation was 1. VPC (observed unbound sum dabigatran model) showed good performance of the model in capturing the central tendency and variability in the ECT data while for the model-predicted moieties, the VPC captured the central tendency but underpredicted the extent of variability in the ECT data. Since only the fixed effects (or the "typical" subject) were used for the simulations, the model was deemed to be adequate for this purpose.

dTT

The relationship between observed unbound sum dabigatran and dTT was described using a linear slope-intercept model with additive IIV terms on both intercept and slope and additive residual variability. There was a significant effect of Japanese race on the slope and intercept compared to non-Japanese resulting in decreased IIV for slope and intercept and a 63 point decrease in AIC. The intercept also differed pre- and post-idarucizumab administration. With the evaluation of study effects, the effects of Japanese race on slope and intercept were exchanged with corresponding effects of study 1351.5. AIC for the final model was decreased by another 5 points relative to the model including race. All PK/PD parameters were estimated with good precision.

Similar results were obtained for the base model using both model-predicted unbound sum dabigatran and IFSD as the independent variable. However, in the covariate evaluations, only an effect of Japanese race on intercept was identified. With the evaluation of study effects, the effect of Japanese race on intercept was exchanged with a corresponding effect of study 1351.5. All PK/PD parameters were estimated with good precision.

Although goodness of fit plots lacked trend lines, there appeared to be reasonable agreement between observed dTT and both PRED and IPRED dTT values. The ETAs were not correlated and ETAs and residuals appeared uniformly distributed. VPC (observed unbound sum dabigatran model) showed good performance of the model in capturing the central tendency and variability in the dTT data while for the model-predicted moieties, the VPC captured the central tendency but underpredicted the extent of variability in the dTT data. As for ECT, the model was deemed to be adequate for the purpose of simulating the dTT profile for the "typical" subject.

aPTT

The relationship between observed unbound sum dabigatran and aPTT was described using an Emax model (including an intercept) with additive, correlated IIV terms on both intercept and Emax and additive residual variability. There were significant effects of Japanese race on Emax and age on the intercept resulting in decreased IIV for Emax and intercept and a 62 point decrease in AIC. With the evaluation of study effects, the effect of Japanese race on Emax was exchanged with a corresponding effect of study 1351.5 and the effect of age on intercept was exchanged for a corresponding effect of study 1351.2. AIC for the final model was decreased by another 17 points relative to the model including race.

Similar results were obtained for the models using both model-predicted unbound sum dabigatran and IFSD as the independent variable.

For all three models, PK/PD parameters were estimated with good precision. EC_{50} for each dabigatran moiety was estimated towards the upper limit of plasma concentrations represented in the data set (90th percentile for IFSD and 95th percentile for unbound dabigatran) although 95% CI for EC_{50} was within the range of plasma concentrations in the data set.

Although goodness of fit plots lacked trend lines, there appeared to be reasonable agreement between observed aPTT and both PRED and IPRED aPTT values. There was reasonably high correlation between ETAs. ETAs and residuals appeared uniformly distributed. VPC plots for all final aPTT models showed reasonable performance of the models in capturing the central tendency and variability in the aPTT data.

TT

The relationship between observed unbound sum dabigatran and TT was described using an Emax model (including an intercept) with additive IIV on Emax and additive plus power model describing residual variability. There were significant effects of body weight on the intercept and EC_{50} and age on the intercept resulting in decreased IIV for Emax and a 120 point decrease in AIC. With the evaluation of study effects, an effect of study 1321.1 on intercept was identified. Inclusion of this study effect permitted simplification of the residual error model to a power model and resulted in a 146 point decrease in AIC relative to the model without any study effects. Model parameters were re-estimated after exclusion of 3 outliers (absolute value of standardized residuals > 10).

Similar results were obtained for the base models using both model-predicted unbound sum dabigatran and IFSD as the independent variable. In addition to significant effects of body weight on the intercept and EC_{50} and age on the intercept, other covariate effects (including Japanese race) on the intercept were identified. However, the 95% CI for many of these covariate effects included 0 and consideration should have been given to exclusion of these effects from the models. For the model-predicted unbound sum dabigatran and IFSD models after inclusion of study effects, significant covariate effects included study 1321.5, study 1321.1, age and body weight on intercept, age on Emax and body weight on EC_{50}. As for aPTT, EC_{50} for each dabigatran moiety was estimated towards the upper limit of plasma concentrations represented in the data set (95th percentile for all dabigatran moieties) although 95% CI for EC_{50} was within the range of plasma concentrations in the data set.

Although goodness of fit plots lacked trend lines, there appeared to be reasonable agreement between observed TT and both PRED and IPRED TT values. ETA Emax and residuals appeared uniformly distributed. VPC plots for all final TT models including study effects showed reasonable performance of the models in capturing the central tendency and variability in the TT data.

15.3.7.6. Simulations

Results of the simulations based on the final population PK/binding model and PK/PD models for ECT and dTT were presented in tabular and graphical displays and described in the PK/PD report. The findings were as follows:

- Following low idarucizumab doses (1 and 2 g), median IFSD exposure increased with declining renal function for all simulations. At higher doses, median IFSD was generally low, regardless of renal function, due to dabigatran-idarucizumab complex formation.
- Exposures and responses to 2.5 + 2.5 g idarucizumab doses separated by 15 min were similar to those for the single 5 g idarucizumab dose.
- Cmax decreased with increasing doses of idarucizumab and time to the maximum IFSD concentration increased reflecting availability of idarucizumab to bind dabigatran redistributing from peripheral tissue compartments.
- Peak IFSD concentrations were lower in Japanese subjects (40 y, 60 kg) than in Caucasian subjects (40 y, 80 kg) due to higher dabigatran CL/F and increased idarucizumab exposures in Japanese subjects.
- Complete reversal of the anticoagulant effect of dabigatran (220 mg BID DE) occurred at idarucizumab doses of 2.5 + 2.5 g or 5 g for all Caucasian and Japanese subjects and CrCL subgroups. At lower idarucizumab doses (1 and 2 g), the fraction of reversed subjects increased with increasing renal function. For example, incomplete reversal occurred in 18% and 8% of subjects respectively following the lowest idarucizumab dose (1 g) for CrCL = 40 mL/min and CrCL = 120 mL/min, respectively, in typical Caucasian subjects. Incomplete reversal occurred in 12% and 6%, respectively, in typical renally impaired (CrCL = 40 mL/min) and normal renal function (CrCL = 120 mL/min) Japanese subjects.
- Complete reversal of the anticoagulant effect of dabigatran (150 mg BID DE) occurred at idarucizumab doses of 2 g or higher for all Caucasian and Japanese patients (75 y) and CrCL subgroups. At the 1 g idarucizumab dose, the fraction of reversed subjects was 94 – 100% for Caucasians and 98 – 100% for Japanese and increased with increasing renal function.
- At the maximum IFSD effect (i.e., at the time of the peak IFSD plasma concentration) following 2.5 + 2.5 g regimen, 5% of subjects would be expected to have dTT of 6.1 sec and 10.7 sec > 110% ULN for typical Caucasian subjects (40 y, 80 kg) with CrCL = 120 mL/min and 40 mL/min, respectively. These values were 3.1 sec and 6.4 sec, respectively, for typical Japanese subjects (40 y, 60 kg). For typical Caucasian and Japanese patients (75 y), at least 95% of subjects were expected to have dTT < 110% ULN.

Simulation results including IIV in the PK/PD models presented in the PK/PD report were not reviewed because they were outside of the scope of the stated methods and not justified by the modelling results.

15.3.7.7. Results summary

In summary, detailed descriptions of the analysis data sets, PK modelling results and PK/PD modelling results were presented in a logical manner using accepted model building and model evaluation techniques. However, there were some omissions and inconsistencies that hindered interpretation of the results:

- a complete description of the PK data set and exclusions and more granularity in the development of the structural PK model (as recorded in the run log) would have been useful,
- trends in goodness of fit plots were shown using smoothing functions for the PK model but not for the PK/PD models,

- correlations among covariates were illustrated using scatterplots with smoothing functions and correlation coefficients for the PK/PD analysis but not the PK analysis,
- in the PK/PD model evaluation but not the PK model evaluation, sensitivity analyses were conducted to explore the impact of outliers on parameter estimation,
- handling of BLQ idarucizumab plasma concentrations and their impact on PK parameter estimation was not discussed anywhere in the report,
- sensitivity analysis to explore the effect of outliers on parameter estimation was conducted for the PK/PD model evaluation but not for the PK model,
- critical evaluation of the VPC plots to address model deficiencies was lacking.

Application of the models to perform simulations was appropriately justified and presented to address their intended purpose. Overall, the population PK and PK/PD models provided acceptable descriptions of the data and the modelling and simulation results were presented in accordance with EMA guidelines.

15.3.8. Evaluation of discussion and conclusion

Discussion focussed on the principal findings of the modelling and simulation analyses and their clinical implications. Points of discussion and a critique are as follows:

15.3.8.1. Population PK

- Idarucizumab PK was described. The central (Vc) and steady-state (Vss) volumes were estimated to be 3.25 L and 9.24 L for a 75 kg subject, suggesting that idarucizumab is confined to extracellular fluid. It was stated that idarucizumab PK was linear and not altered when bound to dabigatran. However, these assumptions were based on general goodness of fit of the linear model to the data and were not formally tested.

  Idarucizumab CL was reduced in subjects with renal impairment while Vc varied with body weight. An effect of Japanese race on idarucizumab CL was deemed to be not clinically relevant.

- Ultrafiltration was used to exclude quantitation of idarucizumab-bound dabigatran from quantitation of sum dabigatran. However, it also excluded plasma protein bound dabigatran. Consequently, unbound sum dabigatran was quantified and sum dabigatran was derived using the population PK model.

- Both renal function and age were included as covariates on dabigatran CL/F.

  Contrary to the statement that age was an influential covariate, it was included in the model based on previous experience but was not statistically significant nor clinically relevant (8% change in CL/F over 20 – 80 y age range).

  Previously, the relationship between renal function and dabigatran CL/F was characterised using a saturable (Emax) relationship. This model was not tested in the analysis because of the small number of subjects with renal impairment in the analysis data set. Instead, a power model described the decrease in dabigatran CL/F with greater renal impairment.

  It was noted that the rate and extent of dabigatran redistribution after idarucizumab administration were overestimated in subjects with renal impairment. Inclusion of an additional effect of renal impairment on CL/F and Q/F did not substantially improve the model and warrants further evaluation.

- Dabigatran CL/F was increased by 16% in Japanese subjects relative to Caucasian subjects with normal renal function. The difference was not deemed clinically relevant in light of previously published results (Haertter et al., 2011).

- It was noted that previous dabigatran PK models have estimated a large Vc/F relative to Vss/F (Vc/F = 756 L and Vss/F = 1101 L) for an 80 kg subject. However, in the present PK model, Vc/F and Vss/F were estimated to be 278 L and 960 L, respectively, suggesting that the majority of the drug was distributed peripherally not centrally. These estimates derived from the interplay of the amount of drug in the periphery, distributional rate constants and the relative sizes of the central and peripheral compartments influencing dabigatran redistribution after idarucizumab administration and this perturbation of the system may have more accurately reflected dabigatran disposition.

15.3.8.2. Population PK/PD models

- Although not referenced, it was noted that model-predicted sum dabigatran – coagulation biomarker PK/PD relationships were similar to those previously reported. The implications are two-fold: first, there was no clinically relevant effect of idarucizumab on PK/PD relationships (notwithstanding the PK effect of binding dabigatran to render it unavailable in plasma to have an anticoagulant effect). Second, it permits extrapolation of idarucizumab-induced reversal of dabigatran anticoagulant effects to the patient population.
- For models in which unbound sum dabigatran was the independent variable, the slope was reduced by approximately 30% corresponding to 30% lower unbound sum dabigatran concentrations compared to sum dabigatran concentrations.
- For each of the coagulation biomarkers, there was a significant effect of Japanese race. For the most part, the effect of race could be exchanged for an effect of study 1321.5 in addition to other study effects in studies 1321.1 and 1321.2. It was discussed that the effect of race was a surrogate for study effects attributed to bioanalytical differences due perhaps to lot to lot variations in coagulation biomarker assays. The effect of Japanese race remains to be further examined in a patient population (phase 2/3).
- Age, body weight and idarucizumab administration were identified as significant predictors IIV in the PK/PD analyses. However the effect sizes were small and as such could be considered to be clinically irrelevant in the phase 1 population evaluated.

15.3.8.3. Simulations

- Simulations demonstrated complete reversal of coagulation in > 96% Caucasian and Japanese patients (75 y) across a broad range of renal function (CrCL = 40 – 120 mL/min) following single doses of 1 to 5 g or 2.5 + 2.5 g of idarucizumab. There was no apparent difference in response to a single 5 g dose or two 2.5 g infusions separated by 15 minutes.
- Idarucizumab was effective over a broad range of renal function. Since CL of idarucizumab and CL/F of dabigatran were both reduced in renal impairment, there may be increased opportunity for binding and therefore efficacy was predicted to be maintained despite renal impairment.

  The stated conclusions clearly summarised the key points made in the discussion. These were succinct and appropriately summarised the main findings of the study.

15.4. Summary and Implications of findings

15.4.1. Summary of findings

Analyses conducted to characterise the population PK of idarucizumab, its binding interaction with dabigatran and extrinsic factors that may influence idarucizumab PK. In addition, dabigatran's effect on coagulation biomarkers and the possible influences of extrinsic and treatment-related factors were investigated using a population analysis approach. The methods used were generally appropriate and adequate for their purpose.

On the basis of this evaluation, it was concluded:

- A population PK model was developed to describe the disposition of idarucizumab and dabigatran when administered alone and in combination in healthy subjects. The base and final PK models were verified. Effects of significant covariates identified in the analysis, including age, body weight, renal function and race, remain to be validated in a patient population.
- Unbound dabigatran plasma concentrations were substantially decreased in the presence of idarucizumab due to the formation of an idarucizumab-dabigatran complex. While the model captured the binding interaction, there was some misspecification of the model during the dabigatran redistribution phase that warrants further review of the model. Dabigatran redistribution from the peripheral to the central compartment was attenuated with increasing doses of idarucizumab.
- The primary demographic covariate influencing clearance of both drugs was renal function. As a result, exposures to both idarucizumab and dabigatran may be expected to be increased in renal impairment with increased opportunity for binding. Consequently, idarucizumab efficacy may be expected to be maintained in renal impairment as shown in simulations over a CrCL range of 40 -120 mL/min.
- Notwithstanding the PK effect of binding dabigatran to render it unavailable in plasma to have an anticoagulant effect, the underlying relationship between dabigatran exposure and anticoagulation was unaffected by idarucizumab coadministration. The clinical relevance of the effect of Japanese race on these relationships remains to be further examined in a patient population (phase 2/3).
- Rapid and complete reversal of coagulation was shown to occur in 100% of simulated subjects (40 y and 75 y Japanese (60 kg) and Caucasian (80 kg), CrCL = 40 – 120 mL/min) after a 5 g idarucizumab dose given either as a single infusion or as two 2.5 g infusions 15 min apart. The impact of extremes of body weight by itself and in the presence of renal impairment warrants investigation as both factors significantly influenced idarucizumab disposition.

15.4.2. Implications of findings

The PK and PK/PD analyses conducted included 244 and 189 healthy subjects, respectively, from 3 phase 1 trials. Modelling and simulation results support the administration of 5 g idarucizumab as a single infusion or as two 2.5 g infusions 15 min apart to reverse the anticoagulant effects of steady-state dabigatran (administered as 150 mg or 220 mg BID DE over 4 days). Experience in patients is required to validate the models developed herein using phase 1 data and to provide justification for dosage selection in the clinical setting. Moreover, dose selection must be evaluated in the context of safety data, which was not included in the PK/PD report.

Considerations with regard to the proposed PI are as follows:

- Elderly patients/sex/race and Renal impairment

  Conclusions regarding effects of age, sex, race and renal impairment on idarucizumab exposure based solely on phase 1 data are premature and require validation with patient data. On this basis, they should be qualified as preliminary, or removed. Furthermore, based on phase 1 data, renal impairment and body weight are both important determinants of idarucizumab exposure and consideration should be given to exposures at the extremes of these covariate ranges, separately and together.

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