24 September 2015
EMA/713107/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Praxbind

International non-proprietary name: idarucizumab

Procedure No. EMEA/H/C/003986/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ACT	Activated clotting time
AIC	Akaike information criteria
ADA	Anti-drug antibody
ALT	Alanine aminotransferase
aPTT	Activated partial thrombin time
AST	Aspartate aminotransferase
AUC	area under the curve
AUEC	Area under the effect curve
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
CGE	capillary gel electrophoresis
CHO	Chinese hamster ovary
CI	confidence intervals
CL	clearance
Cmax	maximal concentration
Cov	covariance
CPP	critical process parameter
Cpre,ss	Trough concentration in steady state
CQA	critical quality attributes
CrCl	Creatinine clearance
CT	Computer tomography
CTR	Clinical trial report
CV	coefficient of variation
CWRES	conditional weighted residuals
DE	Dabigatran etexilate
DNA	Deoxyribonucleic acid
DP	drug product
DS	drug substance
DSC	differential scanning calorimetry
dTT	Diluted thrombin time
DV	dependent variable
DVT	Deep vein thrombosis
EBE	empirical Bayes estimates
EC50	drug concentrations to achieve 50% of the maximum effect
ECT	Ecarin clotting time
EDQM	European Directorate for the Quality of Medicines and Healthcare
EMA	European Medicines Agency
Emax	maximum observed or estimated efficacy or PD effect
Epsilon (ε)	residual variability in NONMEM
EST	estimation ($estimation)
Eta (η)	interindividual variability in NONMEM
F	absolute bioavailability
Fab	antigen-binding fragment
Fc	crystallizable fragment
FMEA	failure mode and effect analysis
FOCE	first-order conditional estimation (estimation method in NONMEM)
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HC	heavy chain
HCP	host cell protein

HMWCs	High molecular weight compounds
HPLC-MS/MS	high-performance liquid chromatography tandem mass spectrometry
HPSEC	high performance size exclusion chromatography
ICH	International Committee on Harmonization
ICH	Intracranial haemorrhage
Ida	Idarucizumab
IFSD	idarucizumab-free sum dabigatran
IIV	interindividual variability
IMP	importance sampling (estimation method in NONMEM)
IPRED	individual prediction
ITS	iterative two-stage (estimation method in NONMEM)
IWRES	individual weighted residual obtained as the difference between observed concentration and IPRED scaled by the within-individual standard deviation of the measurement
Ka	absorption rate constant
Kd	dissociation constant
kD	kilodalton
Kdeg	degradation rate constant
koff	degradation rate constant
kon	association rate constant
ksyn	synthesis rate constant
LC	light chain
LC-MSMS	liquid chromatography-tandem mass spectrometry
LLOQ	Lower limit of quantitation
LMWs	Low molecular weight species
LoQ	List of Questions
LTBS	log transform both sides
MAT	Median absorption time
MCB	master cell bank
MVM	Minute Virus of Mice
N	Number
NaCl	sodium chloride
NONMEM	non-linear mixed effects modeling program
OFV	objective function value
OMEGA (ω2)	intersubject variance
PD	Pharmacodynamics
PE	Pulmonary embolism
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
popPK	population pharmacokinetics
PPCB	end of production cells
PPQ	process performance qualification
PRED	population predicted value
PRV	Pseudorabies Virus
PV	process validation
Q	inter-compartmental clearance (central-peripheral)
QbD	quality by design
QD	once daily
QQ	quantile quantile
QTPP	quality target product profile ()
REC	Recommendation
RE-LY	randomized evaluation of long-term anticoagulant therapy
Reo	Reo Virus Type 3
RH	relative humidity
Rho	correlation coefficient

RSE	relative standard error
SAEM	stochastic approximation expectation maximization estimation method in NONMEM
SCE	Summary of clinical efficacy
SD	Standard deviation
SE	standard error
SIGMA (σ 2)	residual variance
SOP	standard operating procedure
SPR	surface plasmon resonance
SS	steady-state flag
Syn	synthesis rate
THETA (θ)	estimate of fixed effect
TIA	Transient ischaemic attack
Tmax	time of maximal concentration
TSE	transmissible spongiform encephalopathy
TT	Thrombin time
ULN	Upper limit of normal
Vcentral	central volume of distribution
Vd	Volume of distribution
Vd,ss	Volume of distribution in steady state
VPC	visual predictive check
VTE	Venous thromboembolic events
WCB	working cell bank
WRES	weighted residuals
WT	body weight
XMRV	Xenotropic murine leukemia virus-related virus
Yo	years old

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 2 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Praxbind, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Praxbind is specific reversal agent for dabigatran and is indicated in patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required:

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Idarucizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0069/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0069/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance idarucizumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP in 15 March 2012, 18 October 2012 and 21 November 2013. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Jens Heisterberg

- The application was received by the EMA on 2 March 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 26 February 2015.
- The procedure started on 26 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 June 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- PRAC RMP advice and assessment overview adopted by PRAC on 9 July 2015.
- During the meeting on 20-23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 August 2015.
- The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Safety/Efficacy assessment of the product:
  - A GCP inspection at two investigator sites in Belgium between 27 -28 May 2015 and 15- 17 June 2015.The summary report of the inspection carried out was issued on 07 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 9 September 2015.
- PRAC RMP advice and assessment overview adopted by PRAC on 10 September 2015.
- During the meeting on 21-24 September 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Praxbind.

2. Scientific discussion

2.1. Introduction

Anticoagulation therapy is a mainstay of treatment and prevention of thrombosis in different clinical settings. Dabigatran etexilate (DE) is an oral prodrug of dabigatran, a direct-acting thrombin inhibitor that received marketing authorization for:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors.
- Treatment of acute DVT and/or PE and prevention of related death
- Prevention of recurrent DVT and/or PE and related death
- Primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

For the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF), treatment with DE demonstrated superior efficacy over warfarin with the 150 mg bid dose with similar bleeding rates and non-inferiority with the 110 mg bid dose, with an improved bleeding profile (RE-LY, U09-3249-02). However, as with all anticoagulants, bleeding was a side effect in the RE-LY trial, with major bleeding events reported in 3.3% and life-threatening bleeding events in 1.5% of patients treated with 150 mg DE bid (yearly event rates). With the increasing use of novel oral anticoagulants such as DE, patients with life-threatening or uncontrolled bleeding can benefit from additional options that could be used in emergency situations in order to reverse the anticoagulant effects of these new drugs.

Idarucizumab is being developed as a specific reversal agent for dabigatran. Idarucizumab neutralizes dabigatran's anticoagulant effect due to its very high affinity for dabigatran (Kd = 2.1 pM). 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 is manufactured from Chinese Hamster Ovary cells, using standard mammalian cell culture and protein purification techniques. The final drug product is a solution for injection filled aseptically into sterile glass vials. Each vial contains 50 mL solution at the concentration of 50 mg/mL. Because idarucizumab is a Fab without the Fc receptor binding fragment of an antibody, no complement-initiated cytotoxic effects or interactions with Fcγ-receptors or neonatal Fc receptors are expected. Idarucizumab is primarily intended for single use. Repeated use with more than 1 day offset of time between the administrations may occur in rare cases.

The proposed indication was for adult patients treated with DE when rapid reversal of the anticoagulant effects of dabigatran is required:

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

The CHMP approved the following indication:

Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:

- *For emergency surgery/urgent procedures*

- *In life-threatening or uncontrolled bleeding.*

2.2. Quality aspects

2.2.1. Introduction

Idarucizumab is directed against the direct thrombin inhibitor dabigatran. Idarucizumab binds to dabigatran with a higher affinity than dabigatran binds thrombin. The biological activity of idarucizumab is determined by a thrombin clotting assay.

The drug product is presented as a solution for injection/infusion containing 2.5 g/50 mL idarucizumab as active substance. Other ingredients are sodium acetate trihydrate, acetic acid, sorbitol, polysorbate 20 and water for injection. The product is available in a 50 mL glass vial (type I glass), with a butyl rubber stopper and an aluminium cap. Although this dossier is not considered a Quality by Design application, certain elements of an enhanced approached were applied. The active substance and finished product are referred to as drug substance and drug product in this report as per CTD.

2.2.2. Active Substance

General information

Idarucizumab is a humanised Fab molecule derived from a murine IgG1 isotype antibody molecule and consists of one κ light chain (LC) and one γ heavy chain fragment (HC). The heavy chain fragment and the light chain are linked together by one disulfide bond between cysteine 225 of the heavy chain fragment and cysteine 219 of the light chain. There are four additional cysteine residues present on each LC and HC fragment that form intramolecular disulfide bridges. The molecule is not glycosylated. Based on the predicted amino acid sequence, the molecular formula of the disulfide bonded idarucizumab Fab molecule is $C_{2131}H_{3299}N_{555}O_{671}S_{11}$.

Manufacture, characterisation and process controls

Manufacture

Idarucizumab drug substance (DS) is produced in Chinese hamster ovary (CHO) cells in two multi-product buildings at the same site at Boehringer Ingelheim Pharma, GmbH & Co KG, Biberach, Germany. Each building contains multiple bioreactors. Multiple drug substance batches manufactured in both buildings may be pooled or single batches may be split, depending on manufacturing needs. The manufacturing process in both buildings is considered comparable.

During multiple inoculum cultivation steps, the cells are repeatedly sub-cultivated to provide sufficient cells to initiate the cell expansion bioreactors. Critical and non-critical process parameters have been defined for the different cultivation of upstream-manufacturing. Harvest is performed by centrifugation. The purification process starts with a capture step. Further steps include a virus inactivating step and purification steps via filtration/ chromatography. Viral filtration, final sterile filtration and formulation finalises the purification process. DS storage conditions have been acceptably justified. The manufacturing process is considered properly described and includes satisfactory in-process controls (including appropriate bioburden and endotoxin control). Appropriate containers are used to store DS to provide protection from light and from microbial ingress.

Control of Materials

Information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented.

The generation of the cell substrate and establishment of the two-tiered cell banking system has been properly described. The master cell bank (MCB), working cell banks (WCB) and end-of-production cells (PPCB) have been tested for ID, purity, viral contamination and presence of the heavy- and light chain cDNA sequences as required in ICH Q5D. Genetic stability has been satisfactorily demonstrated including up to the proposed limit of *in vitro* cell age. The viral testing of the cell banks are in accordance with ICHQ5A. No animal derived components were used in the manufacture of the current MCB and WCB.

Control of critical steps and intermediates

The idarucizumab drug substance manufacturing process is properly described and relevant in-process controls are established. In-Process Control specifications are established for the drug substance manufacturing process for control of sterility, mycoplasma and adventitious virus.

Process parameters (critical, non-critical parameters and key process indicators) and the operating ranges proposed for the drug substance manufacturing process are acceptable. The manufacturing process has been developed in accordance with the principles of ICHQ8, Q9, Q10 and Q11, no design space is however claimed. Key process indicators are, although not ICH terminology, acceptable as they support consistent production. The drug substance process development is described in detail. The process development includes identification of the quality target product profile (QTPP) and critical quality attributes (CQA), followed by risk assessments and performance of several characterisation studies in order to identify critical process parameters and establish the acceptable ranges for the process parameters. Viral safety aspects and microbial contamination control have been established and are acceptable. Process controls for critical steps satisfactorily ensure process performance and achievement of the desired product quality.

Process Validation

The manufacturing process was evaluated and validated by demonstrating that the process, when executed within defined operating parameter ranges and with defined process controls, met pre-established acceptance criteria for specified critical process parameters and key performance indicators and consistently produced product that met release criteria. The definition of process controls and the consequences of not meeting specifications and corresponding limits are acceptable. Regarding the process validation (PV) strategy, acceptance criteria (AC) define the currently known acceptable criterion of a critical parameter.

An appropriate number/ scale of batches were studied in process validation. Media preparation was also validated.

The idarucizumab fermentation process is considered well validated supporting that a consistent and robust fermentation process is in place. All pre-defined ranges for process parameters (critical, key- and non-critical) were met for all validation batches. All release specifications for the drug substance were met as well (after purification).

During the subsequent commercial scale production campaign), although overall, pre-specified target and acceptance criteria were met, some deviations were observed in two runs. Corrective actions are underway but the final outcomes will be reported as recommendations, as committed to by the applicant (see discussion). This is acceptable.

The validation of the purification process also included data on buffer preparation, process step yields, sanitary processing, stability of intermediate pools, microbial control, clearance of the process related impurities, column and membrane regeneration, column carry-over and membrane cleaning, re-filtration of the virus filtered pool and drug substance pool, splitting and pooling of the drug substance, extractables/ leachables and freeze/ thaw of the drug substance. In conclusion, the data show that the process is capable of producing drug substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria.

Manufacturing process development

Drug substance batches throughout development and for the to-be-marketed product have been identically formulated at a concentration of 50 mg/mL.

The manufacturing process development for idarucizumab drug substance and drug product has been satisfactorily described. Main changes introduced during process development cover the site and scale of manufacture and introduction of a new MCB and WCB. Remaining changes are considered adjustments to scale-up and process optimisation. Non-clinical batches were produced by an early process but lots representing this material were included in comparability studies. Lots manufactured using further optimised manufacturing processes have been used in clinical and stability studies. The final, optimised process will be used for commercial manufacturing and drug substance produced by this process is intended to be used for marketed product. The comparability studies cover the full process development from the initial process to the final commercial process. This is acceptable.

A comprehensive set of data is presented from the comparability studies. In general, the comparability studies consist of comparison of release data, additional characterisation, process-related impurity removal and forced degradation stability studies. The data presented fully support comparability of material throughout the idarucizumab manufacturing process development.

Characterisation

For the elucidation of structure and physicochemical characteristics of idarucizumab, relevant parameters such as secondary structure and higher order structure, identity (primary structure), heterogeneity and purity aspects have been addressed, and the molecule was appropriately characterised.

Regarding impurities, data are shown for several validation runs at commercial scale. All data are well within the specification, supporting that the process is capable of removing impurities. Product-related impurities are molecular variants of the active molecule that can arise during manufacture of the drug substance or during storage. These have been appropriately identified and qualified.

Potential process-related impurities include DNA and host cell protein (from the CHO cells) and other impurities from the cell-culture/ purification processes. Residual DNA levels are below the WHO limit of < 10 ng DNA per maximal dose and host cell proteins (HCP) comply with the defined limits. Adequate methods have been used for the analysis of all impurities. Consistent removal of process-related impurities has been sufficiently demonstrated and validated. Finally, stated impurities have been studied in clinical studies and are acceptably qualified.

Specification

The specification controls appearance/description (colour/opalescence), pH, osmolality and quantity as well as safety/contaminants (endotoxin, bioburden), identity, purity tests (charge and size variants), impurity and potency (thrombin clotting assay and Fab binding activity assay). Drug substance specifications are considered acceptable. Analytical methods have been adequately described and validated.

Batch analysis

Release results from lots including several full scale, final-process, commercial batches are presented in the dossier. The release data across processes and within batches are consistent and comparable and in compliance with the specification. Results therefore confirm consistency of the manufacturing process.

Reference materials

As defined by ICHQ6B, an in-house reference material has been established for idarucizumab. Qualification of the current reference standard involved appropriate quality control tests as well as specified characterisation tests. The protocol for the establishment of working reference standards is acceptable.

Stability

Stability data at long-term storage conditions at -20°C have been recorded for several commercial primary stability batches. The analytical methods used for assessing stability are a subset of the drug substance release methods and are considered stability indicating and acceptable.

No significant changes were observed for any of the test parameters under the long-term storage conditions studied. All results met the proposed shelf life specifications.

Based on the data provided, an 18 month shelf-life can be accepted for storage of drug substance at -20°C or three months for storage at 2-8°C. A time of 30 days at 25°C is acceptable for drug substance during processing. For future extension of shelf-life, an acceptable post approval change protocol has been provided.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Idarucizumab bulk drug substance is formulated in a buffer consisting of acetic acid, sodium acetate, sorbitol and polysorbate 20 in water for injection at a pH of 5.5. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation, neither are there any excipients of human or animal origin present in the drug product (DP).

The intended commercial formulation is not identical to that used in clinical studies but has been adequately justified since the changes from the clinical formulation have been supported by sufficient data to show comparability at the quality level. The primary packaging is a 50 mL glass vial (type I glass), with a butyl rubber stopper and sealed with an aluminium flip-off cap. The material complies with Ph.Eur. and EC requirements.

The monosaccharide sorbitol was selected to adjust the tonicity of the formulation. The results of the screening showed that the materials which are used for production of idarucizumab drug product have no leachables of toxicological concern.

Boehringer Ingelheim has followed a development approach as described in ICH Q8 (R2). A quality target product profile (QTPP) was compiled for idarucizumab solution for injection/infusion. Based upon this, critical quality attributes CQAs have been identified for DS and DP to assure that the QTPP specified will be met. Standard risk assessment tools were employed to identify possible significant inputs and outputs of the process. Risks were assessed with respect to identified critical quality attributes. Data generated throughout development, at all scales, were used to support classification of process parameters and performance indicators and to identify acceptable ranges. The control strategy, based on the product and

process characterisation have been detailed. The QbD approach does not seem, in all respects, to comply with the ICH approach and it noted that a design space is not claimed. However, the overall number and nature of CQAs and critical process parameters (CPPs) identified are reasonably expected for a product and process such as this. In addition, the process ranges proposed are relatively narrow and do not allow for high production flexibility. The pharmaceutical development has been described from laboratory to commercial scale with the identification of critical process parameters and their normal and acceptable operating range.

The pharmaceutical development has been described in sufficient detail and in compliance with the ICH guideline Q8(R2) on pharmaceutical development.

Manufacture of the product and process controls

Idarucizumab drug product manufacturing includes thawing of formulated drug substance, optional splitting and pooling to yield an adequate amount for aseptic filling, followed by sterile filtration and filling, capping, visual inspection, labelling, and secondary packaging. All formulation is completed as part of drug substance manufacture. Idarucizumab drug product sterile filtration and filling is performed under aseptic conditions. All production areas and personnel performing aseptic operations are monitored on a routine basis. Adequate in-process controls are defined which include critical tests for bioburden/ endotoxin control. Hold times for drug substance in the stainless steel container and hold times for drug product are defined. Finished product storage and shipment conditions have been defined. The manufacturing process has been validated.

The DP validation data demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. There are no new impurities introduced during manufacture of DP.

Product specification

The DP specification controls appearance/description (colour/opalescence/clarity/particles), pH, osmolality, polysorbate 20 content, and extractable volume as well as safety/contaminants (endotoxin, bioburden), identity, purity tests (charge and size variants), impurity (endotoxins, sterility), potency (thrombin clotting assay and Fab binding activity assay) and container closure integrity. Drug product specifications are considered acceptable. Analytical methods have been adequately described and validated.

Batch analysis

Concurrent with the drug substance process changes, the drug product also underwent manufacturing changes. All data obtained at the time of release comply with the testing specification in effect at the time of release and confirm consistency of the manufacturing process. All data obtained comply with the proposed commercial testing specification and the drug substance and product assessments concluded that the Praxbind drug product produced from all processes through development is comparable.

Reference materials

The same reference standard is used for drug product and drug substance testing

Stability of the product

The stability program includes batches manufactured for clinical use and for primary stability, including process validation lots. Stability data have been submitted at the long-term storage condition at 2 - 8°C for multiple lots throughout development. Data have not been submitted using the ultimate commercial process for DS however the differences between this and the other processes used during development

are considered minor and well-justified by the applicant by submission of comparability data. These data are therefore considered representative of the final, full-scale commercial scale process.

Idarucizumab drug product has demonstrated high stability at the intended long-term storage temperature. The currently claimed shelf-life of 24 months is acceptable although according to ICH Q5C, stability information should be provided on at least 3 batches of final container product representative of that which will be used at manufacturing scale. However, the provided data are considered acceptable because of the medical need for this product, as assessed by CHMP, and given the other supporting data provided. Data have been provided to support three months for processing and handling of drug product at 25°C, by the Company, prior to marketing.

Studies have been conducted to support the storage period claimed just prior to use. The data presented support storage at maximum 25°C for 48 hours prior to use. Finally, data have been provided to support storage of the solution once it has been removed from the vial. Chemical and physical in-use stability has been demonstrated for 1 hour at room temperature.

Stability data submitted show no significant change in product during storage and support the proposed shelf life. In accordance with EU GMP guidelines[2], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Adventitious agents

TSE compliance: idarucizumab is produced from recombinant CHO cells which are cultivated in serum-free medium. Satisfactory information has been provided on animal-derived materials used in the cell culture media. The MCB and WCB used for the idarucizumab manufacturing process are prepared without any materials of animal origin. All excipients are of non-animal origin. During cell cloning, materials of animal and human origin have been used which were shown to have negligible TSE risk.

In summary, Compliance with the TSE guideline EMEA/410/01 rev 03 has been sufficiently demonstrated. The current MCB/WCB and the drug product are therefore free from TSE-risk substances.

Virus safety: idarucizumab is produced from recombinant CHO cells. The manufacturing processes of two specified animal-derived reagents used during fermentation include steps which are able to inactivate viruses. All other reagents used at the manufacturing process and during cell banking are of non-animal and non-human origin. Several reagents of human and animal origin have been used at cell line development. They have been shown to be sufficiently safe regarding adventitious virus by appropriate donor selection, animal veterinary control and/or by reduction of viruses in their manufacturing process. The idarucizumab cell banks were extensively tested for adventitious viruses including specific tests for bovine, porcine and ovine viruses and for endogenous viruses in accordance with ICH Q5A (R1). No adventitious viruses have been detected. The only viruses found were A-type retrovirus-like particles in the MCB and post production cell bank (PPCB) by transmission electron microscopy analysis. Yet, CHO cells are well known to produce those particles, which have been shown to be non-infectious. A satisfactory report for cell bank testing has been provided.

Additionally, several batches for commercial use have been produced, which are routinely tested for adventitious viruses and retrovirus particles. No viruses have been found to date. The presence of retrovirus-like particles in the MCB is acceptable because there is sufficient capacity in the downstream purification process of idarucizumab to reduce such virus particles. Appropriate model viruses have been used in the virus validation studies. The choice of model viruses has been satisfactorily justified, since they represent a variation in resistance to physical and chemical agents or treatments. All tested model viruses have been satisfactorily reduced, and the calculated safety factor per dose show that the purification process of idaruzicumab is able to reduce the level of virus to a negligible level. Virus reduction steps include chromatography, low pH treatment and virus retentive filtration. The comparison

of the scale-down model and the process scale showed no significant differences between small scale and process scale for all unit operations. In summary, the virus safety for idarucizumab has been sufficiently demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general, the manufacturing process has been satisfactory described and has been validated by demonstrating that the process, when executed within defined operating parameter ranges and with defined process controls, meets pre-established acceptance criteria for specified critical process parameters and key performance indicators and consistently produces product that meets release criteria. The specification test panel is considered sufficient. The applicant has applied QbD principles in the development of the drug substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance or for the finished product. Two recommendations have been raised regarding issues raised from data submitted from DS manufacturing runs. The reasons for the observed results from two failed fermentation runs have been satisfactorily explained. The recommendations relate to reporting back to confirm that all agreed corrective actions are now in place. The company accepted both recommendations.

The most critical point raised in the D120 LoQ was the amount of sorbitol used as excipient in the formulation of the DS/DP. This is extremely high (40 mg/mL, 2000 mg per dose) and might have an impact on patient safety. The applicant recognises the risk of the rather high amount of sorbitol excipient in one single dose of idarucizumab (4g) and has provided clinical justification for its use. In summary, there is a calculated risk that 1 in 10 patients with hereditary fructose intolerance (HFI) who are treated with idarucizumab will suffer a possible severe outcome. This has to be weighed against the risk of prolonged severe bleeding.

Since idarucizumab is intended to be administered undiluted as an emergency treatment, the formulation must contain a tonicity agent at physiological concentrations. In general, the concentration of sorbitol used is common for saccharides as the tonicity agent in formulations of biologicals that are administered parenterally and undiluted. Other tonicity agents stabilised idarucizumab to a lesser degree than sorbitol, as stated by the applicant. Also the applicant concludes that the decision to use sorbitol as the tonicity agent in the current idarucizumab formulation is supported by the fact that sorbitol is chemically inert at the target pH.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP has recommended points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical pharmacology program was designed to characterize: (1) the specificity and affinity of idarucizumab for dabigatran and its active glucuronide metabolites; (2) the inhibition of dabigatran anticoagulant effects in vitro and in vivo; and (3) the potential binding of idarucizumab to other thrombin substrates to induce potential prothrombotic effects. In addition, (4) effects of idarucizumab on dabigatran-associated blood loss in a large animal trauma model were investigated. Potential (5) effects of idarucizumab on anticoagulants other than dabigatran, on antiplatelet agents or on binding to dabigatran during hemodilution or in the presence of coagulation factor concentrates were also tested.

The nonclinical pharmacokinetic program was designed to investigate the pharmacokinetics (PK), pharmacodynamics (PD), and urinary excretion of idarucizumab in rats and monkeys in the absence and the presence of dabigatran, as well as the effects of various dosage regimens of idarucizumab on the PK/PD and urinary excretion of dabigatran or sum dabigatran (the sum of dabigatran and its glucuronides). In addition, the impact of renal insufficiency on the PK/PD and urinary excretion of idarucizumab and dabigatran was investigated using the 5/6 nephrectomized rat model.

The nonclinical toxicology studies were designed to evaluate the potential toxicity of idarucizumab in rats and monkeys in GLP studies of up to 4- and 2-weeks of daily treatment, respectively. As the proposed use of idarucizumab in humans is to neutralize the anticoagulant effects of DE, studies in monkeys additionally explored potential toxicity of idarucizumab on a background of DE. Safety pharmacology studies to investigate cardiovascular, respiratory, and central nervous system (CNS) effects were conducted. All GLP toxicity studies used idarucizumab proposed commercial formulation.

Binding of idarucizumab with human tissues was tested in a tissue cross-reactivity (TCR) study, as was binding to rat and monkey tissues. Local tolerance of the idarucizumab proposed commercial formulation was evaluated following intravenous and perivascular administration, and hemolytic potential in human blood was assessed. In addition to evaluations routinely conducted as part of toxicity studies, the general toxicity studies included additional measurements of anti-idarucizumab and anti-dabigatran antibodies, thrombotic activity, effects on coagulation indices, circulating immune complexes, and immune complex deposition. No genotoxicity, carcinogenicity, or reproductive toxicity studies have been conducted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacology in vitro

Idarucizumab was shown to bind to dabigatran with a high affinity of 2.1 pM, which is > 300-times more potent than the binding affinity of dabigatran for thrombin. Due to the long half-life of the resulting idarucizumab:dabigatran complex, this binding is practically irreversible. Binding at pH 6.7 is still in the low pM range, indicating that idarucizumab should capture dabigatran even under conditions of acidosis.

Idarucizumab inhibited the anticoagulant activity of dabigatran in vitro as demonstrated in a modified thrombin time assay. In human plasma, the IC50 was 3.1 nM in the presence of 7 nM dabigatran, the IC50 was 10.9 nM in the presence of 30 nM dabigatran. Idarucizumab reversed the anticoagulant activity of the active dabigatran metabolites. The inhibition of the anticoagulant effect was comparable in plasma and

whole blood, indicating a low non-specific binding to other cellular components in blood. In an in vitro model of haemostasis, addition of idarucizumab to blood previously treated with dabigatran restored the level of fibrin and platelet coverage to normal levels.

By X-ray crystallography, the dabigatran binding site of idarucizumab was found to be structurally similar to the thrombin active site. Nevertheless, idarucizumab did not bind to other thrombin substrates, (such as FV, FXIII, protein C, vWF, S-2238) or human plasma or serum albumin. Furthermore, idarucizumab did not have thrombin-like enzyme activity as demonstrated in several thrombin-dependent coagulation assays. In line with these findings, in vivo PD and toxicity studies did not provide evidence for a pro-thrombotic activity of idarucizumab.

Primary pharmacology in vivo

Reversal of the anticoagulant activity in vivo was shown in rats which had been pre-treated with dabigatran to achieve therapeutically relevant dabigatran plasma levels (approx. 300 nM). In this model, a single bolus of idarucizumab at a dose equimolar to the total dabigatran dose immediately reversed the anticoagulant activity of dabigatran and maintained the activity over a period of 30 minutes. Of note, plasma levels of total dabigatran increased by 10-fold upon idarucizumab administration. However, as there was no anticoagulant activity present, this represented dabigatran bound to idarucizumab. Since dabigatran is present in the extravascular compartment as well as in blood, and idarucizumab is predominantly restricted to plasma, the observed elevation of plasma total dabigatran probably represents the redistribution of dabigatran from extracellular space in tissues into the blood compartment.

The antidote activity of idarucizumab was further demonstrated in several bleeding models: In a tail bleeding model in rats, the dabigatran-induced prolongation of bleeding time was rapidly reversed by a single bolus injection of idarucizumab. This was associated with an immediate reduction of plasma active dabigatran and an approx. 7-fold increase in plasma total dabigatran. To model dabigatran overdose situations, rats had been pre-treated to achieve supra-therapeutic plasma concentration of dabigatran. Also in this situation, anti-coagulation and bleeding time was reversed by idarucizumab. When an initial idarucizumab dose was not sufficient to completely block active dabigatran, administration of a second idarucizumab dose shortly later completely inhibited the dabigatran effect and normalized bleeding.

The effect of idarucizumab on dabigatran-associated bleeding in emergency situations was evaluated in pig model of liver trauma. In this study, idarucizumab stopped bleeding and prevented mortality associated with blood loss. The changes in hemodynamic and hypo-perfusion parameters associated with haemorrhagic shock, were reversed and anti-coagulation was normalized. Overall, the effect of idarucizumab was immediate and dose-dependent. Complete reversal of anticoagulant activity was observed at an idarucizumab dose that was equimolar to the total body load of dabigatran. Under these conditions, inhibition of anti-oagulation was maintained for several hours and prevented also bleeding from a second site of injury afflicted 1 hour after the administration of idarucizumab. A single idarucizumab dose lower than equimolar to the total dabigatran body load was not able to maintain inhibition of anticoagulant activity over time. In consequence a low dose of idarucizumab was able to achieve haemostasis at the initial wound site, but not at a later occurring second wound site. Nevertheless, in this situation a second dose low of idarucizumab can reverse the remaining anticoagulation and stop bleeding from the new wound site. In addition, idarucizumab was shown to reverse the dabigatran effect in a model of intracranial bleeding in mice.

Specificity of idarucizumab for dabigatran

As volume expanders are used in patients with severe blood loss, a potential effect of routinely used volume replacement agents (HES, gelatin or red blood cells) on the idarucizumab activity was studied in

anticoagulated pigs under severe blood loss. In this model, administration of idarucizumab immediately blocked the dabigatran activity and there were no differences between the various volume expander groups. Thus, routine volume expanders do not interfere with the idarucizumab activity.

Potential interference of coagulation factor concentrates with the idarucizumab activity was evaluated in vitro in human plasma. The presence of prothrombin complex concentrates (PCC), activated PCC, or recombinant FVIIa had no effect on idarucizumab-mediated reversal of the dabigatran-mediated anti-coagulation. The applicant has sufficiently explained that tThe concentrations of PCC, aPCC and rFVIIa used in the in vitro experiments correspond to the circulating in vivo concentrations of these factors when given to patients at the recommended doses. It was agreed that these concentrations were clinically relevant.

In a tail bleeding study, it was evaluated to what extent idarucizumab affects bleeding in rats anti-coagulated with dabigatran plus anti-platelet agents (i.e. aspirin, clopidogrel or ticagrelor). In this study, idarucizumab normalized dabigatran-induced bleeding time, even in animals concomitantly treated with an anti-platelet agent. However, it was unclear, if any of the anti-platelet agents (at the dose used) had an effect on rat tail bleeding time at all, since there was no difference in bleeding time between the rats treated with dabigatran and those treated with dabigatran plus anti-platelet reagent. The applicant has justified the doses of the antiplatelet agents used as active were based on reduction of platelet function by aggregometry. In the absence of data on bleeding time in animals treated with anti-platelet reagent alone this was considered acceptable.

It was further evaluated if idarucizumab inhibits the anticoagulant effect of other oral or parenteral anti-coagulants. Idarucizumab did not affect the activity of anti-coagulants with mode of action different to that of dabigatran (i.e factor Xa inhibitors, heparin or vitamin K antagonist) and the activity of the direct thrombin inhibitors hirudin and argatrobon. However, idarucizumab did inhibit the anticoagulant activity of melagatran, a DTI which is structurally similar to dabigatran. However, this effect was not clinically relevant since melagatran was not commercially available.

Secondary pharmacodynamic studies

No specific pharmacology studies were performed to investigate secondary pharmacodynamic effects. Idarucizumab was designed to bind specifically to dabigatran and in itself is not enzymatically active. The lack of thrombin-like effects of idarucizumab was tested as part of the primary non-clinical pharmacology focusing on the mechanism of action. The absence of pro-thrombotic effects in vivo was tested at part of toxicology and clinical studies. Further secondary PD studies were not considered necessary.

Safety pharmacology programme

The core battery safety pharmacology evaluations conducted on idarucizumab are listed below.

Table 1. Overview of safety pharmacology studies with idarucizumab.

Organ system: Test (GLP status)	Species	Dose (mg/kg)	Parameters	Results
Cardiovascular: Cardiovascular function (GLP)	Rhesus monkey	0, 12/150, 12/500, 0/500, 12/0 [a]	HR, ECG	No effects
CNS: Modified Irwin (GLP)	Rat Crl:WI(HAN)	0, 150, 500 intravenous	modified FOB, motor activity	No effects

Organ system: Test (GLP status)	Species	Dose (mg/kg)	Parameters	Results
Respiratory: plesthymography (GLP)	Rat (Wistar-Han) (males)	0, 150, 500 intravenous	respiration rate, tidal volume, minute volume	No effects

ECG = electrocardiogram; FOB = functional observational battery; HR = heart rate.

a Dabigatran etexilate/idarucizumab, administered orally/intravenously. Intravenous administration occurred 1.5 hours after oral dosing.

In line with ICH S6(R1) inclusion of cardiovascular and CNS safety pharmacology assessment was included into GLP repeated-dose toxicity studies. There were no test-article-related effects on cardiovascular functions, as evaluated in rhesus monkeys, and respiratory or CNS functions as evaluated in rats.

Pharmacodynamic drug interactions

Potential interactions with other anti-coagulants or anti-platelet agents or coagulation factor concentrates was tested and reported in the primary pharmacology section since this is related to idarucizumab specificity and part of its mechanism of action. Potential interactions with other anti-coagulants are sufficiently evaluated.

2.3.3. Pharmacokinetics

The PKs of idarucizumab after IV administration were evaluated in single-dose PK studies and in the repeated-dose toxicity studies in rats and rhesus monkeys in the absence and presence of dabigatran. In addition, PK of dabigatran and PD endpoints were evaluated.

Bioanalytical methods:

For quantification of idarucizumab in plasma and urine from rats, rhesus and pigs the same sandwich ELISA format was developed and validated. Presence of dabigatran did not interfere with quantification of idarucizumab.

A validated LC-MS/MS method was used for measurement of dabigatran and sum dabigatran in plasma and urine samples from rats, rhesus and pigs. Presence of idarucizumab did not interfere with quantification of dabigatran.

For detection of anti-idarucizumab antibodies in rat and rhesus plasma a bridging ECL assay was developed. However, false positive results were detected with this assay due to reactivity of dabigatran acyl glucuronides with the detection reagents. An additional ECL-assay with new bridging reagents was then developed and validated which did not result in false positive results in monkeys treated with dabigatran alone.

A radio-immuno-precipitation assay (RIPA) was developed for detection of anti-dabigatran antibodies in rhesus plasma. The screening assay was adequately validated, but found to be sensitive to the presence of dabigatran and to idarucizumab. Together with the confirmatory assay and the characterization of positive samples with an anti-idarucizumab idiotype mAb the RIPA is considered suitable for use.

For detection of anti-coagulant activity in rat and rhesus plasma, three different assays were validated: the diluted thrombin time (dTT), the activated partial thromboplastin clotting time (aPTT), and the ecarin clotting time (ECT). These assays had been previously validated for human plasma. The re-validation to support the change in matrix is considered adequate.

For detection of pro-thrombotic activity, two commercially available ELISA assays were validated for use in rhesus plasma, one for detection of D-dimers and the other for detection of pro-thrombin fragment 1+2 (F1+2). Both assays can be considered suitable for use in rhesus plasma; however there precision at the lower concentration range is limited.

Absorption:
In both rats and rhesus monkeys, the PK and TK characteristics of idarucizumab after IV administration were typical for a Fab. Exposure (Cmax and AUC0-24) increased in a dose-proportional manner, and remained unchanged following repeated daily dosing. The plasma concentration-time profile was biphasic with a rapid initial decline phase and a slow terminal phase, with a half-life of approx. 6 hrs in rats and 4-5 hrs in rhesus monkeys. The clearance of idarucizumab was low and the volume of distribution was small. In both species, there were no differences in the idarucizumab PK parameters in the absence or presence of dabigatran treatment.

The plasma profile of dabigatran in rats, when administered alone, was biphasic. However, upon administration of idarucizumab there was a rapid increase in dabigatran plasma concentration, due to re-distribution from tissue to plasma. Thus, the volume of distribution was smaller, dabigatran clearance was lower, and MRT was slightly reduced in rats treated with idarucizumab compared to rats treated with dabigatran alone.

In rhesus monkeys receiving oral DE, dabigatran glucuronides contributed substantially to the overall sum dabigatran exposure. In general, dabigatran and sum dabigatran exposure in monkeys after PO dosing was rather variable, likely due to the low oral bioavailability. Nevertheless, following administration of idarucizumab, exposure to dabigatran and sum dabigatran increased substantially, indicating re-distribution of dabigatran and its glucuronides from tissues to plasma.

Reversal of anti-coagulant activity was detectable immediately after administration of idarucizumab. Complete reversal of the anti-coagulant activity was maintained over a period of 24 hrs when the idarucizumab concentration was equal to or larger than the concentration of sum dabigatran.

A PK/PD model was developed and validated based on data from the rhesus monkey PK/PD study. When using this model to simulate exposure of sum dabigatran and active dabigatran in the presence of idarucizumab in healthy humans and in pigs with trauma, the simulated and measured data (e.g. for active dabigatran) were mostly in line. In study conditions where there appeared to be slight differences between the simulated data and the means of the measure data, the model under-estimated the idarucizumab effect, which is considered a conservative approach.

Excretion
A small fraction of idarucizumab (15-20% in rats, approx. 10% in rhesus) is eliminated by renal excretion. This is in line with literature data for other proteins with a molecular weight < 60kDa. Of note, renal excretion of idarucizumab is not affected by the presence of dabigatran.

In rats, a major fraction of dabigatran (approx. 60%) is excreted into urine. In contrast, in rhesus only a minor fraction of dabigatran (< 2%) is recovered from urine which is likely due to the low oral bioavailability of dabigatran etexilate. In both species, the extent of dabigatran renal excretion is not impacted by the presence of idarucizumab.

The effect of renal impairment on the PK and urinary elimination of idarucizumab and dabigatran was evaluated in 5/6 nephrectomised rats. Renal impairment results in reduced clearance (approx. 50%) and increased exposure of both, dabigatran and idarucizumab. For dabigatran, urinary excretion is a major pathway of elimination, which was reduced from 45% to 32% in renally impaired rats. In contrast, for idarucizumab, urinary excretion was only slightly reduced (15.8% to 12.6%) in renally impaired rats. These data indicate that the overall reduction in idarucizumab clearance is mainly due to reduction of

catabolism and not a reduction of excretion of idarucizumab by the kidney. Importantly, idarucizumab reverses the anti-coagulant activity of dabigatran even under conditions of renal impairment.

2.3.4. Toxicology

Toxicity studies with idarucizumab were performed in rats and rhesus monkeys. All studies in monkeys were conducted in the absence and presence of DE. Rhesus monkeys were considered the most relevant species based on non-clinical studies with dabigatran, the target for idarucizumab. Dabigatran half-life of dabigatran is similar in rhesus and humans, while it is much shorter in rats. Furthermore, rhesus monkeys generate the active glucuronide metabolites of dabigatran, whereas in rats this is negligible. An overview of the toxicity studies is provided in the table below. The selection of rhesus monkeys as relevant species for toxicity studies is justified.

All studies were conducted under GLP except for the single-dose study in rats and the escalating-dose study in rhesus monkeys.

Table 16. Overview of toxicity studies with idarucizumab

Study (GLP status)	Species	DE/Idarucizumab Dose (mg/kg)[a]	Main Result[b]
Single dose (non-GLP)	Rat	0/0, 0/50, 0/175	No adverse effects
4-week with 4-week recovery (GLP)	Rat	0/0, 0/150 & 0/500	NOAEL = 0/500 mg/kg/day Cmax MoE = 7 AUC MoE = 3
Escalating dose (non-GLP)	Rhesus monkey	0/0, 0/30, 0/90, 0/175 and 12/30, 12/90, 12/175	No adverse effects
2-dose with 14-day recovery (GLP)	Rhesus monkey	0/0, 12/150, 12/500, 0/500, 12/0	NOAEL = 0/500 mg/kg Cmax MoE = 9 AUC MoE = 6 NOAEL = 12/150 mg/kg Cmax MoE = 2 AUC MoE = 1
2-dose with 14-day recovery, renal focus (GLP)	Rhesus monkey	0/0, 12/500, 0/500	NOAEL = 0/500 mg/kg Cmax MoE = 6 AUC MoE = 5 NOAEL = 12/500 mg/kg Cmax MoE = 7 AUC MoE = 5
2-week with 28-day recovery and 3-day DE re-admin (GLP)	Rhesus monkey	0/0, 12/150, 12/500, 0/500	NOAEL = 0/500 mg/kg/day Cmax MoE = 7 AUC MoE = 5 NOAEL = 12/500 mg/kg/day Cmax MoE = 7 AUC MoE = 5
Local tolerance – perivascular (GLP)	Rabbit	5 mg (0.1 mL of 50 mg/mL)	No local effects observed.
Tissue cross-reactivity (GLP)	Human, rat, Rhesus monkey	2 and 10 µL/mL	No binding observed.
Hemolysis of blood (non-GLP)	Human	125 µL of 50 mg/mL in 0.5 mL	No hemolysis observed.

a Expressed as dabigatran etexilate (DE)/ idarucizumab; DE administered orally and Ida administered intravenously 1.5 hours later.

b NOAEL = no observed adverse effect level. MoE = multiple of exposure. Multiples were calculated based on exposure in 45 – 64 year healthy volunteers in clinical trial 1321.2.

Single dose toxicity

Single-dose toxicity study in rats [U12-3325, non-GLP]

This study was performed to assess the systemic toxic potential and toxicokinetics of idarucizumab, when administered by a single intravenous bolus injection. Three groups of rats (n=10/sex/group) received idarucizumab at 0, 50 or 175 mg/kg; satellite groups (3/sex for control; 9/sex/group for treatment groups) were used for TK analysis. Animals were necropsied 48 hrs after treatment.There were no changes in clinical signs, body weight, food consumption, hematology, coagulation, organ weights, macroscopic and microscopic evaluations. Mean triglyceride values were elevated 1.5- and 1.8-fold in males treated with 50 or 175 mg/kg, respectively. There was no effect of treatment on any other clinical chemistry parameter. Idarucizumab exposure (Cmax and AUC0-24) increased approximately dose-proportionally and was similar between male and female rats.

Combined male and female maximum plasma concentrations (Cmax) were 18,150 nM (867 µg/mL) and 60,050 nM (2,870 µg/mL) and exposures (AUC0-24) were 7,105 nM*h (340 µg*h/mL) and 24,050 nM*h (1150 µg*h/mL) at 50 and 175 mg/kg, respectively. In conclusion, idarucizumab was well tolerated. However, after a single dose of idarucizumab, a dose-related increase in triglyceride compared to controls was observed. The increased mean triglyceride levels were observed in male rats 24 hours after they were administered a single dose of 50 or 175 mg/kg idarucizumab, whereas a similar change was not observed in female rats. The cause of the triglyceride increase was not investigated. In contrast, no change in triglyceride levels were observed in male and female rats administered idarucizumab at 150 and 500 mg/kg/day for 28 days. Consequently, the increase in triglyceride observed in the single-dose rat study was considered transient and likely spurious. No changes in triglyceride levels have been observed in the three studies conducted in monkeys.

Repeat dose toxicity

Rat toxicity studies

In the 4-week rat study, the main finding was a dose-dependent decrease in plasma urea and creatinine levels. This was judged to be non-adverse even though levels were still decreased in males as compared to controls at the end of the recovery phase. Higher than control thymus weights (absolute, relative to brain and relative to body weight) were recorded for female rats receiving 150 or 500 mg/kg/day. The Applicant provided additional discussion regarding the treatment-related changes in urea, creatinine and thymus weight and further substantiated setting the NOAEL at 500 mg/kg in this study. This was considered acceptable.

Rhesus toxicity studies

Toxicity studies in rhesus monkeys consisted of a non-GLP escalating dose study with idarucizumab doses up to 175 mg/kg and two GLP studies with idarucizumab given 2 times at doses up to 500 mg/kg IV on a background of oral vehicle or dabigatran etexilate followed by a 14-day recovery period. In the first 2-day study, the systemic exposure to idarucizumab in animals receiving 500 mg/kg idarucizumab was considered to be higher than in the subsequent monkey studies for animals dosed with the same dose level. It was determined to be due to the rate of intravenous administration of idarucizumab. Importantly, the concentrations of idarucizumab solution used in all three studies were comparable. In addition, a GLP 2-week study was performed, with repeated daily IV administration of idarucizumab (up to 500 mg/kg) on a background of daily oral vehicle or dabigatran etexilate, followed by a 28-day recovery period and a 3-day re-administration of oral vehicle or dabigatran etexilate.

In general, idarucizumab was well tolerated in rhesus monkeys at doses up to 500 mg/kg IV in the absence and presence of dabigatran. In 2 of the studies, there were renal findings with unclear relationship to treatment in individual monkeys: In the initial dose-escalation study, there were histopathological findings in the kidneys of 2 monkeys treated with idarucizumab alone but not in monkeys treated with the combination of idarucizumab and dabigatran etexilate. In a 2-dose study, there were blood chemistry and histopathological findings in one recovery male treated with dabigatran etexilate and idarucizumab high-dose. The findings in this animal were consistent with an impairment of renal function; however, low body weight of the animal and elevated protein in urine already prior to treatment suggest that the animal may have had other health problems already pre-study. Importantly these renal findings were not repeated in the other 2-dose study and the 2-week study. Thus, kidneys are not considered a target organ of toxicity for idarucizumab.

In theory, development of anti-drug antibodies can result in the generation of immune complexes which may be deposited in the kidneys and cause renal problems. This possibility was evaluated in depth in the 2-week study. In this study anti-idarucizumab antibodies were detected in some of the animals at the end of treatment and also at the end of the recovery period. However, there was no evidence for the development of anti-dabigatran antibodies. Circulating immune complexes were within normal limits in all animals and there was no evidence for immune complex deposition in the kidneys as evaluated by immunohistochemistry.

Apart from general toxicity, the 2-week study in rhesus monkeys also investigated the potential for pro-thrombotic activity of idarucizumab. Based on D-dimer and F1+2 evaluation, there was no evidence for a pro-thrombotic effect of idarucizumab.

During infusion of idarucizumab to one male monkey in the three-phase PK/PD study (U12-3849, U13-3539), the animal collapsed, possibly due to a hypersensitivity reaction, and was subsequently euthanized. Microscopic examination of the lungs revealed severe haemorrhage in the alveolar spaces and bronchioles with hyperplasia and fibrosis of the alveolar walls and pleura, the latter indicating a pre-existing condition. The Applicant states that hypersensitivity reactions are frequent in non-human primates repeatedly dosed with human antibodies and that the lung and GI tract findings occur spontaneously in non-human primates due to chronic inflammation, infections, or parasite infestations.

In summary, the NOAEL in rhesus monkeys treated with idarucizumab in the absence or presence of dabigatran for 2 days or 2 weeks was 500 mg/kg/day. The resulting exposure multiples, taking into account different human populations (healthy, elderly, with renal impairment) were approx. 5-7x based on Cmax and 3-6x based on AUC0-24. This was considered sufficient.

Based on the nature of the product and its mechanism of action, omission of genotoxicity studies and carcinogenicity studies was accepted. It was also agreed that reproductive and developmental toxicity studies are not warranted taking into consideration the proposed used of idarucizumab on single days in emergency situations.

Idarucizumab, in the proposed commercial formulation was well tolerated locally when given via the intravenous route to rats and rhesus monkeys or via the paravenous route to rabbits. However, the presence of sorbitol (at 220 mM) in the formulation was considered a risk for patients with hereditary fructose intolerance (HFI) hence a warning was included in the SmPC.

Toxicokinetic data

Idarucizumab exposure was similar between both sexes in rats and monkeys and was comparable following single and repeated doses. A similar Cmax was achieved between rats and monkeys at idarucizumab doses levels of 150 and 500 mg/kg but the AUC0-24 in the rat was approximately half of the AUC0-24 in monkeys. This is consistent with a faster clearance in rats than in monkeys.

For calculation of exposure multiples, mean Cmax and AUC values (combined males and females) from the indicated animal studies are used. Exposure multiples were calculated for different human populations (healthy, elderly, with renal impairment) as they differ in exposure to idarucizumab. Across the different animal studies and human populations there is an approx. 5-7x exposure margin based on Cmax and 3-6x exposure margin based on AUC. This is considered sufficient.

Local Tolerance

Local tolerance to the idarucizumab after IV injection was assessed by microscopic examination of the injection sites as part of the GLP toxicity studies (28 day treatment in rats, up to 14 days in rhesus). There was no evidence of an idarucizumab-related effect.

Perivascular tolerance was evaluated in a dedicated study New Zealand White rabbits. Three animals were administered slow bolus, perivascular injections of 0 and 5 mg idarucizumab (dose volume of 0.1 ml) in the right and left ears, respectively, in proximity to the marginal ear vein. Paravenous injection was well tolerated; there were no systemic or local effects based on dermal and microscopic evaluations. Toxicity studies indicate that idarucizumab is locally well tolerated when given intravenously or paravenously.

Other toxicity studies

Tissue cross-reactivity

The target for idarucizumab is the small molecule pharmaceutical dabigatran which is not present in human or animal tissues. Thus, the absence of tissue binding by idarucizumab is not surprising.

Haemocompatibility

The proposed specification for the impurity “kappa select” in idarucizumab drug substance (<13 ng/mg) is based on the available toxicity data for kappa select protein and was considered acceptable.

Excipients

The applicant justified a content of 40 mg/ml sorbitol as acceptable even for patients with Hereditary fructose intolerance (HFI) based on a publication from Mock et al. (1993). However, this limit has been derived for oral intake of fructose, in contrast while parental administration of sorbitol has been recognized to be potentially lethal [Cox et al., 1993].

The applicant acknowledged a risk for patients with HFI, and proposed a warning statement in section 4.4 of the idarucizumab SmPC. The proposal of contraindicating idarucizumab in patients with HFI was discussed since idarucizumab administration could be fatal for patients with HFI. At the end it was agreed to include a warning rather than a contraindication that in patients with HFI the risk of treatment with idarucizumab must be weighed against the potential benefit of such an emergency treatment. If idarucizumab is administered in these patients, intensified medical care during idarucizumab exposure and within 24 hours of exposure is required.

2.3.5. Ecotoxicity / environmental risk assessment

The Fab idarucizumab is a protein which is unlikely to result in significant risk to the environment. This was agreed by the CHMP.

2.3.6. Discussion on non-clinical aspects

Idarucizumab is a humanized Fab which is developed as an antidote to the direct thrombin inhibitor dabigatran. Idarucizumab is intended to be administered to patients in emergency situations to reverse the anti-coagulant effect of dabigatran. The pharmacology of idarucizumab was adequately demonstrated *in vitro*. Idarucizumab binds with high affinity to dabigatran and thereby blocks the anti-coagulant activity of dabigatran in human plasma. Absence of idarucizumab binding to other thrombin substrates and lack of pro-thrombotic activity was sufficiently demonstrated as considered by the CHMP.

Blockade of the dabigatran anti-coagulant activity and its effect on bleeding was demonstrated in several in vivo models. The rat tail bleeding model represents a situation with limited blood loss. Also the intracranial haemorrhage in mice is associated with limited bleeding. In contrast, the pig liver trauma model is associated with severe blood loss, haemorrhagic shock and ultimately mortality. This large animal model allows studying the PK/PD of idarucizumab under “controlled” blood loss and under concurrent emergency treatments administered in case of bleeding (e.g. volume expanders). As it is difficult to obtain controlled information from humans treated in emergency situations, these non-clinical PD studies were considered justified and the results were adequately reflected in section 5.1 of the SmPC.

Specificity of idarucizumab for dabigatran was demonstrated, since idarucizumab did not inhibit the anti-coagulant activity of other oral or parenteral anti-coagulants. Potential interference of coagulation factor concentrates or anti-platelet reagents with the idarucizumab activity was evaluated.

PK and toxicity of idarucizumab was evaluated in rats and rhesus monkeys, in the absence and presence of dabigatran. Given that the metabolism of dabigatran was similar in rhesus monkeys and humans, rhesus were considered the more relevant species for assessing human risk. PK of idarucizumab in rats and monkeys was typical for a Fab, with a dose-dependent increase in exposure, small volume of distribution and a short half-life. Consistent with a molecular weight below 60 kDa, idarucizumab was eliminated via the kidneys, the majority via renal metabolism and only a small portion (approx. 10% in rhesus) via renal excretion. PK of idarucizumab was not affected by the presence of dabigatran. In contrast, the PK of dabigatran was substantially impacted by the presence of idarucizumab. Immediately upon idarucizumab injection, there was an increase in dabigatran plasma concentration due to re-distribution of dabigatran from tissues into blood. However, when the idarucizumab concentration was high enough (at least equimolar to the total dabigatran body load), anti-coagulation remained reversed.

The exposure to dabigatran is increased in patients with renal impairment. Thus, the activity of idarucizumab was studied in a rat model of renal impairment. In this model, there was a reduced clearance of both dabigatran and idarucizumab and consequently an increased exposure of both substances. Importantly, idarucizumab reversed the anti-coagulant activity of dabigatran under conditions of renal impairment.

A PK/PD model was developed and validated based on data from the rhesus PK/PD study. This model simulated well the exposure to dabigatran in the presence of idarucizumab in healthy humans and in pigs with liver trauma.

Toxicity of idarucizumab was evaluated in rats (in the absence of dabigatran) and in rhesus monkeys (in the absence and presence of dabigatran). Overall, idarucizumab was well tolerated in these studies. In rats, the NOAEL was 500 mg/kg/day, given daily for 4 weeks; in rhesus monkeys, the NOAEL was 500 mg/kg/day on a background of 12 mg/kg/day dabigatran, when given once daily for 14 days. Based on these NOAELs sufficiently high exposure multiples compared to different human populations (healthy, elderly, with renal impairment) are achieved, ranging from 5-7x based on Cmax and from 3-6x based on AUC0-24.

2.3.7. Conclusion on the non-clinical aspects

Preclinical data reveal no special hazard for humans based on repeated dose toxicity studies of up to four weeks in rats and two weeks in monkeys. Safety pharmacology studies have demonstrated no effects on the respiratory, central nervous or cardiovascular system. Studies to evaluate the mutagenic and carcinogenic potential of idarucizumab have not been performed as based on its mechanism of action and the characteristics of proteins no carcinogenic or genotoxic effects were anticipated. Studies to assess the potential reproductive effects of idarucizumab have not been performed. No treatment-related effects have been identified in reproductive tissues of either sex during repeat dose intravenous toxicity studies of up to four weeks in the rat and two weeks in monkeys. Additionally, no idarucizumab binding to human reproductive tissues was observed in a tissue cross-reactivity study. Therefore, preclinical results did not suggest a risk to fertility or embryo-fetal development. No local irritation of the blood vessel was observed after i.v. or paravenous administration of idarucizumab. The idarucizumab formulation did not produce haemolysis of human whole blood *in vitro*. From the non-clinical point of view the marketing authorisation application for idarucizumab was considered approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. A routine GCP inspection of 2 clinical investigator´s sites in Belgium was requested. Compliance with GCP and applicable regulations was asked to be verified, in particular where it had impact on the validity of the data or the ethical conduct of the phase III study RE-VERSE AD. No specific concerns were identified at the time of adoption of the inspection request. No significant or serious findings or concerns were found during the inspections of both sites and no specific follow up actions for these two sites were recommended. The quality of data was reliable.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study[a]	Study No. [Report No.]	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, PD	1321.1 [c02093109]	5.3.4.1	To investigate safety, tolerability, and PK of iv doses of idarucizumab (SRD) To explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran (EDF)	Randomised, double-blind, placebo-controlled within dose groups	Part 1: 20 mg, 60 mg, 200 mg, 600 mg, 1.2 g, 2 g, 3g, 4 g, 6 g and 8 g Ida or placebo as 1 h infusion; 1g, 2 g and 4 g Ida or placebo as 5 min infusion Part 2: 1, 2, 4 g Ida or placebo as 5 min infusion with pretreatment of 220 mg DE bid for 3.5 days Part 3: 5 g + 2.5 g Ida or placebo (1 h apart) each as 5 min infusion with pretreatment of 220 mg DE bid for 3.5 days	157	Healthy male subjects	Single dose of idarucizumab or placebo DE: Day 1 to 3 bid, Day 4 single dose	Complete; Full

Type of Study[a]	Study No. [Report No.]	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, PD	1321.2 [c02742738]	5.3.4.1	Safety, tolerability, PK and PD of idarucizumab and to establish the idarucizumab dose(s) effective to reverse the dabigatran-induced prolongation of the blood coagulation time	Randomised, double-blind, placebo-controlled, 2-way crossover, single dose	Ida or placebo: 1 g (elderly subjects, subjects with mild RI), 2.5 g (healthy subjects aged 45-64 years), 5 g (healthy subjects aged 45-64 years, elderly subjects, subjects with mild RI), 2x2.5 g (subjects with moderate RI) Redosing with 2.5 g Ida in healthy subjects aged 45-64 years at 2 months after first infusion pretreatment with 220 mg DE bid for 3.5 days in subjects without RI Redosing with 220 mg DE bid for 2.5 days at 24 h after the infusion (medium and high dose/healthy [45-64 years])	46	Healthy male and female subjects aged 45-64 years or elderly (65-80 years); male and female subjects with mild or moderate RI	According to the 2-way crossover design, single dose of idarucizumab or placebo per period DE: Day 1 to 3 bid, Day 4 single dose	Complete; Full

Type of Study[a]	Study No. [Report No.]	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, PD	1321.5 [c03026940]	5.3.4.1	To investigate safety, tolerability, and PK of iv doses of idarucizumab To explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran	Randomised, double-blind within dose groups, placebo-controlled, sequential rising order	Part 1: 1, 2, 4 g Ida or placebo as 5 min infusion; 8 g Ida or placebo as 1 h infusion Part 2: 1, 2, 4 g Ida or placebo as 5 min infusion; 2x2.5 g Ida or placebo (15 min apart). Pretreatment with 220 mg DE bid for 2x3.5 days	80	Healthy Japanese male subjects	Single dose of idarucizumab or placebo DE: per period Day 1 to 3 bid, Day 4 single dose	Complete; Full

Type of Study[a]	Study No. [Report No.]	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK, PD	1321.3 [c03124096] [c03603109]	5.3.4.2	Demonstrate reversal of the anticoagulant effect of dabigatran	Open label, uncontrolled, case series	Idarucizumab total dose of 5 g, given as 2x2.5 g within 15 min, injection/infusion	123 (interim) [200-300 patients targeted per protocol]	Patients treated with dabigatran etexilate who have uncontrolled or life-threatening bleeding requiring urgent intervention, and in patients treated with dabigatran etexilate who require emergency surgery or other invasive procedure	Single dose	Ongoing; Interim

Abbreviations:

id: twice daily dosing
DE: Dabigatran etexilate
EDF: Exploratory dose finding
iv: intravenous
g: gram
h: hour
mg: milligram

min: minute
PD: pharmacodynamics
PK: pharmacokinetics
RI: renal impairment
SRD: single rising dose

[a] Studies which used human biomaterials are not listed.

2.4.2. Pharmacokinetics

The clinical pharmacology of idarucizumab has been investigated in 3 **Phase I trials**: one study in healthy male volunteers (1321.1), one study in healthy male Japanese volunteers (1321.5) and one study in healthy, male and female, mid-aged or elderly subjects as well as subjects with mild or moderate renal impairment (1321.2), a total of 283 healthy volunteers. Of these, 6 subjects had moderate renal impairment (CrCl ⩾30 to <60 mL/min), 12 had mild renal impairment (CrCl ⩾60 to <90 mL/min) and 16 were elderly (65-80 years).

In addition, a **Phase III study** in patients is currently ongoing (study 1321.3, RE-VERSE AD; cut-off date for second interim analysis submitted within current application: 1 April 2015). In the initial submission, pharmacokinetic (PK) information for N=13 patients from study 1321.3 was included (first interim analysis), corresponding to less than 5 percent of the planned up to 300 patients. These patients were sub-divided into group A (bleeding patients) and B (patients requiring urgent surgery), respectively. The majority of patients were older than 65 years (n= 23, 88.5%), and 7 (27%) were older than 85 years. According to a results of the second interim analysis of RE-VERSE AD, a PK data set of N=90 patients was available. Data from n=68 patients were valid with respect to data on creatinine clearance at baseline and complete plasma concentration profiles. Thereof, N=12 had normal renal function (CrCL >80 ml/min), N=26 mild (50-80 ml/min), N=20 moderate (30-50 ml/min), and N=10 severe (0-30 ml/min) renal impairment, respectively.

Idarucizumab is administered intravenously. Doses of 20 mg to 8 g of idarucizumab were administered throughout the clinical program for idarucizumab, administered either as single infusion of 1 h or 5 min, or as two 5 min infusions 15 or 60 minutes apart.

PK in healthy volunteers:

Idarucizumab concentration profiles after 1 hour infusion of doses between 20 mg to 8 g in healthy volunteers in the presence and absence of dabigatran were evaluated by non-compartmental analysis. After infusion of idarucizumab doses ⩾1 g to healthy volunteers in the absence of dabigatran, the calculated distribution volume in the steady state after idarucizumab infusion (Vss) was small ranging from 5.27 to 8.86 L. Idarucizumab was rapidly eliminated from plasma after infusion. In healthy subjects, total clearance ranged between 35.7 and 53.9 mL/min. Plasma concentrations declined to less than 5% of maximal concentrations within 4 hours after end of the 5 min infusions. The terminal half-life ranged from 4.5 to 10.8 hours.

Relevant amounts of unchanged idarucizumab were detected in urine after administration of idarucizumab doses ⩾1 g. The fraction of idarucizumab dose eliminated unchanged into urine increased with dose (range in non-asian healthy subjects 10.7 % to 40.2 % for total idarucizumab doses from 1 to 8 g), suggesting saturation of re-uptake processes in the kidney with higher idarucizumab doses. Renal impairment had no relevant effect on the fraction of idarucizumab dose excreted unchanged into urine. No deviation from dose-linearity was observed for peak and total idarucizumab exposure for doses from 20 mg to 8 g in healthy volunteers. No time dependent effects were observed.

Presence of dabigatran did not appear to majorly influence elimination at higher doses of idarucizumab. There is however a trend of dabigatran to decrease Cmax and increase plasma clearance of idarucizumab in the 1g dose cohort, possibly due to a more apparent influence of target-mediated elimination.

Population PK analysis

Data from n=244 subjects in the three Phase I studies were used to develop a population model describing the kinetics of bound and unbound idarucizumab and dabigatran. “Total idarucizumab”, “sum dabigatran” and “unbound sum dabigatran” were used as dependent variables. A 3-compartment fixed effects model was found to adequately describe idarucizumab kinetics across a wide range of doses, from 20 mg to 8 g, administered as 5- or 60-min long intravenous infusion. As expected with a macromolecule of this size, idarucizumab appears to be confined to extracellular fluid, with the steady state Vd of 9.2 L, exceeding the typical plasma volume (3-5 L). The model estimate for idarucizumab clearance was 2.3 L/h. A terminal half-life of approximately 12 hours was deduced from the model parameters.

CrCL (on CL) and body weight (on Vc) were found to be the only covariates with influence on idarucizumab PK. Sex, age and body weight were not significantly correlated with idarucizumab clearance once CrCL was added to the model. Body weight was found to influence central volume of idarucizumab distribution. There was no relevant effect of age on key idarucizumab PK parameters when compared between subjects aged 45-64 years and elderly subjects aged 65-80 years (n=30).

Plasma exposure of idarucizumab was slightly increased in Japanese compared to Caucasian healthy male subjects. The difference was negligible after normalization for body weight.

Limited information was available on the impact of ADA development on PK of subsequent dosing. Most healthy volunteers enrolled in the PK studies 1321.1, 1321.2 and 1321.5 received a single dose. Information on re-exposure was available from six healthy subjects, who all did not develop ADAs. However, in 25 of 222 healthy volunteers, pre-existing ADA with cross-reactivity to idarucizumab were detected (11%). These data did not indicate a relevant effect of ADA presence on idarucizumab exposure.

Dabigatran disposition after oral administration was best described with a linear, two compartment model. Age was a predictor of dabigatran clearance even after adjusting for the effects of renal function. Sex and body weight were not significantly correlated with dabigatran clearance once CrCL was added to the model. Dabigatran clearance was approximately 16% higher in Japanese subjects relative to Caucasian subjects with normal renal function; for those with mild to moderate renal impairment the difference was just 8%. No other significant covariate effects were observed. Although determined over a limited distribution range, the covariate effects are consistent with previous findings.

The precision of the parameter estimates was generally good, and the values are in the range of previously observed data for dabigatran. However, relatively high inter-individual variability of the absorption parameters (fraction and mean absorption time) and distribution volumes of dabigatran exists. Moderate inter-individual variability (IIV) was estimated for CL (11.9%) and Vc (14.8%) of idarucizumab. High IIV of 322% for a peripheral volume (Vp) of idarucizumab was estimated.

PK in the target population:

In the initial submission, pharmacokinetic (PK) information for N=13 patients from the ongoing study 1321.3 was included, corresponding to less than 5 percent of the planned up to 300 patients. These patients were further sub-divided in N=6 and N=7 for group A (bleeding patients) and B (patients requiring urgent surgery), respectively. In these patients, the sum dabigatran concentration at baseline (before idarucizumab treatment) was low but highly variable between patients, with a median concentration of 71.7 ng/mL (range, 6.9- 795 ng/mL). The corresponding unbound sum dabigatran concentration was 50.0 ng/mL (range, 4.4-643 ng/mL). After the infusion of the first vial of idarucizumab, unbound sum dabigatran concentrations had already decreased to $\leqslant$1.2 ng/mL (LLOQ: 1 ng/mL) in all patients. Unbound sum dabigatran concentration remained at or below the LLOQ over the entire observation period of 24 hours in most patients. The resulting very limited data set indicated some potential differences in the PK of idarucizumab between the two treatment groups.

The available after second interim analysis of RE-VERSE AD more mature dataset of N=90 was used to re-assess the PK of idarucizumab in the two treatment groups. The geometric mean curves were almost superimposable, suggesting no difference between the PK of idarucizumab in the two treatment groups.

Overall, the profiles from phase I treatment groups were similar to the gMean profile from the patients with normal renal function (CrCL ≥ 80 mL/min), indicating similar PK in patients and healthy volunteers with normal renal function.

Special populations

PK in renal impairment

A comparison of the PKs in healthy male and female volunteers with subjects with mild (CrCl ⩾60 to <90 mL/min) and moderate (CrCl ⩾30 to <60 mL/min) renal impairment in study 1321.2 showed a decrease in total plasma clearance with decreased renal function to 69.6% and 54.6%, respectively and a corresponding increase in idarucizumab exposure (AUC0-∞) by 43.5% and 83.5%. Population PK results suggest this relationship to be approximately linear over the range of renal function evaluated in the Phase 1 trials. There was no relevant impact of renal impairment on urinary excretion of unchanged idarucizumab.

The gMean plasma concentration-time profiles from the currently available 90 patients from study 1231.3 separated by creatinine clearance confirmed the dependency of idarucizumab PK in patients on renal function.

AUC0-24 was calculated for above mentioned patient groups with PK data available up to 24 hours, as well as for volunteers in study 1321.2, including volunteer with mild and moderate renal impairment :

Table 39: 2 Descriptive statistics of AUC_{0-24} following administration of 5 g idarucizumab to patients as well as median CrCL from interim 1321.3 by renal function. Clearance categories as used in study 1321.2.

Clearance categories [mL/min]	AUC_{0-24} [nmol*h/L]					CrCL [mL/min]
	N	(Median)	Min	Max	gMean (gCV%)	(Median)
0- < 30	10	133000	87500	200000	129000 (26.1)	19.2
30- < 60	31	74500	38600	153000	76900 (31.0)	46.8
60- < 90	16	53000	40300	88500	54400 (21.6)	69.3
≥ 90	11	42900	24600	80400	43200 (33.4)	126

The data based on n=68 patients/volunteers grouped in four renal function categories (Table 39:2) indicated that geometric mean idarucizumab exposure (AUC0-24h) increases by 26 % in subjects with mild (CLCr 60-90 ml/min), by 78 % in moderate (30-60 ml/min) and by 199% % in severe (0-30 ml/min) renal impairment. Thus, in moderately impaired patients there is an almost 2fold increase of exposure, in severely impaired patients there is even a 3fold increase in exposure.

PK in hepatic impairment

The effect of hepatic impairment on idarucizumab PK has not been investigated. Due to the predominantly renal elimination of idarucizumab, a clinically relevant impact of hepatic impairment on idarucizumab PK is not expected.

Anti-idarucizumab antibodies and Anti-dabigatran antibodies

In all 3 Phase 1 studies, **antibody formation against idarucizumab** following single administration was analysed throughout the study, including a 3-month follow-up period. Overall, a low immunogenic potential, i.e. low incidence of treatment-emergent anti-idarucizumab antibodies and generally low titers, was observed.

Two doses of idarucizumab were administered to 6 volunteers approximately 2 months apart in study 1321.2. However, no anti-idarucizumab antibodies were detected before either administration and at the time of PK and PD assessments. Because all other subjects in the clinical Phase 1 studies received only one dose of idarucizumab (in some cases the dose was administered as two 5 min infusions 15 min or 60 min apart), the effect of treatment-emergent anti-idarucizumab antibodies on the PK of idarucizumab could not be studied. For the subject who had pre-existing antibodies with cross-reactivity to idarucizumab, there was no obvious effect on idarucizumab PK.

The formation of **anti-dabigatran antibodies** was explored in all 3 Phase 1 studies. In total, 43 of 574 samples (7.5%) across trials 1321.1, 1321.2, and 1321.5 were screened putative positive with the modified TT assay. In each trial, some subjects had putative positive responses at the predose visit (overall 10 of 141 subjects, 7.1%), and these are considered to be false positive.

22 of the 141 subjects who were pre-treated with DE before infusion of idarucizumab had developed possible anti-dabigatran antibodies. 10% had a possibly persistent responses and 5.7% had transient responses. However, none of the samples had a strong enough response to completely block the anticoagulant effect of 7 nM (i.e. 3.3 ng/mL) dabigatran. The median steady state concentration of dabigatran (150 mg bid dose) was 390 nM (i.e. 184 ng/mL) in the RE LY study.

Pharmacokinetic interaction studies

PK interaction with dabigatran

The interaction between idarucizumab and dabigatran is the intended effect of idarucizumab. Median exposure to sum dabigatran (total amount [bound & unbound] of dabigatran in plasma plus total amount [bound & unbound] of dabigatran metabolites [glucuronides] in plasma) at peak was comparable or higher in all studied populations, compared to both treatments in the RE-LY study (pivotal study for DE in the AF indication). Dabigatran had no effect on the PK of idarucizumab but idarucizumab had an effect on dabigatran PK. Idarucizumab neutralizes sum dabigatran by binding to it and thus diminishing the unbound sum dabigatran concentration, triggering a new equilibrium whereby dabigatran from tissues re-distributes into plasma. This results in apparently high sum dabigatran concentrations, whereby sum dabigatran is bound in the idarucizumab:dabigatran complex and neutralised. Importantly, this observation coincides with a reduction of unbound sum dabigatran concentrations to levels around the lower level of quantitation as well as abolished or nearly abolished anticoagulation. The idarucizumab-dabigatran complex follows the same elimination route as idarucizumab alone. Idarucizumab binds unbound dabigatran immediately. A dose of 2 g idarucizumab was calculated to be approximately equimolar to median dabigatran body load. In the plasma, dabigatran is bound and neutralized by idarucizumab as long as free idarucizumab is available. For how long free idarucizumab is available (durability of the effect) is dependent on dabigatran body load and the idarucizumab dose. As long as the molar concentration of idarucizumab exceeds the molar concentration of sum dabigatran, all dabigatran in plasma is bound to idarucizumab. Age, sex and renal function had no relevant influence on the effect of idarucizumab on sum dabigatran exposure.

Distribution

Idarucizumab exhibited multiphasic disposition kinetics and limited extravascular distribution. Following the intravenous infusion of a 5 g dose, the geometric mean volume of distribution at steady state (Vss) was 8.9 L (geometric coefficient of variation (gCV) 24.8 %).

Elimination

Idarucizumab was rapidly eliminated with a total clearance of 47.0 mL/min (gCV 18.4 %), an initial half-life of 47 minutes (gCV 11.4 %) and a terminal half-life of 10.3 h (gCV 18.9 %). After intravenous administration of 5 g idarucizumab, 32.1 % (gCV 60.0 %) of the dose was recovered in urine within a collection period of 6 hours and less than 1 % in the following 18 hours. The remaining part of the dose is assumed to be eliminated via protein catabolism, mainly in the kidney. After treatment with idarucizumab proteinuria has been observed. The transient proteinuria is a physiologic reaction to renal protein overflow after bolus/short term application of 5g idarucizumab intravenously. The transient proteinuria usually peaked about 4 h after idarucizumab administration and normalised within 12-24 hours. In single cases the transient proteinuria persisted for more than 24 hours.

Dose proportionality and time dependencies

No deviation from dose-linearity was observed for peak and total idarucizumab exposure for doses from 20 mg to 8 g in healthy volunteers. No time dependent effects were observed.

2.4.3. Pharmacodynamics

Mechanism of action

Idarucizumab is a specific reversal agent for dabigatran. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran with an affinity 300-fold more potent than the binding affinity of dabigatran for thrombin. The idarucizumab-dabigatran-complex showed a very rapid on-rate and slow off-rate of dabigatran to idarucizumab which results in a half-life of the idarucizumab-dabigatran complex of approximately 260 h. Approximately 20% of the absorbed dose of dabigatran is further metabolised in humans into glucuronides, which have equivalent anticoagulant activity to the parent drug. Idarucizumab also binds and reverses the effects of these acylglucuronides of dabigatran with a similar potency range as for dabigatran.

Primary and Secondary pharmacology

The primary PD readout for idarucizumab was reversal of dabigatran-induced anticoagulation. To support this readout, central laboratory analysis of several clotting assays was employed, minimizing analytical variability between studies. Primary focus was on dTT and ECT, whereas aPTT and TT served as supportive measures. In addition, ACT was determined as a bedside test. These tests are available in the clinic and have proven suitable tools in the assessment of anticoagulant activity.

To determine whether infusion of idarucizumab in the absence of dabigatran had any pro-thrombotic effects and to provide further support of reversal of dabigatran mediated effects, ETP was determined both in the absence of dabigatran and after combined treatment. D-Dimer and Prothrombin Fragment 1+2 (F1.2) were explored in 1321.1 and 1321.5 after administration of idarucizumab in the absence of dabigatran.

Further, in study 1321.1, an exploratory marker of bleeding was tested to determine whether it correlated with reversal of anticoagulation. Therefore, the ability of dabigatran to inhibit fibrin formation at a wound site induced by standardized cuts by measuring fibrinopeptide A (FPA) in blood as it exits the wound site

was explored and it was further tested whether idarucizumab could restore fibrin formation at the wound site. As a further readout for bleeding, the washed blood assay was explored.

In Studies 1321.1 and 1321.5 in the absence of dabigatran, dTT, ECT, aPTT, TT and ACT remain consistently comparable before and after infusion of idarucizumab. These findings suggest that idarucizumab has no direct effect on the coagulation cascade. Likewise, in study 1321.1 in the absence of dabigatran, ETP parameters derived before and after idarucizumab and placebo infusion were comparable. This suggested that idarucizumab has no prothrombotic activity. Analyses of D-dimer and Prothrombin Fragment F1.2 after infusion of idarucizumab in the absence of dabigatran did not reveal a prothrombotic signal.

In studies 1321.1, 1321.2 and 1321.5, a total of 141 subjects received dabigatran etexilate co-administered with idarucizumab or placebo. Based on the results of previous studies, reversal of dabigatran anticoagulation was determined either by reaching a back-calculated value from the PK/PD relationship corresponding to 20 ng/mL or by reaching “mean + 2*SD” of available pre-dose measurements. This was considered the ULN.

In study 1321.3, which included patients rather than healthy volunteers and where increased variability of data was thus expected, a higher ULN was defined (110% of the ULN from 1321.2 based on mean + 2*SD). This is considered acceptable by the CHMP.

Primary, secondary and exploratory biomarkers

The primary PD biomarkers were dTT and ECT as these parameters had adequate sensitivity, were the least variable and displayed a linear relationship with dabigatran concentrations. Simultaneously, TT, aPTT and bedside ACT were analysed as supportive measures.

dTT: Across studies, a prolongation of dTT by approximately 2-fold around Cmax was observed following dabigatran administration. All tested doses of idarucizumab resulted in a return to ULN and a dose-dependent durability of effect was seen.

ECT: Across studies, a prolongation of ECT by approximately 3-fold of mean ECT was observed following dabigatran administration. All tested doses of idarucizumab resulted in a return to ULN and a dose-dependent durability of effect was seen. Thus, the results of analyses of the primary PD biomarkers dTT and ECT demonstrate the ability of idarucizumab to reverse the anticoagulant effect of dabigatran. This effect was consistently sustained by administration of a dose of 5 g idarucizumab. Administration of dabigatran increased the mean thrombin lag time ratio and the time to peak ratio while the effect on thrombin peak ratio and thrombin AUC ratio was less pronounced. Across studies, administration of idarucizumab resulted in a dose-dependent reversal of effect of dabigatran on all ETP parameters, i.e. the respective ratios returned to approximately 1. Thus, reversal of dabigatran-induced effects on thrombin generation as measured ty ETP was achieved following idarucizumab administration.

TT: Administration of dabigatran resulted in approximately 10-fold or higher prolongation of mean TT coagulation times at Cmax. Across studies, administration of idarucizumab resulted in a dose-dependent return of TT-values to ULN. In contrast to the other coagulation measurements, durability of effect of idarucizumab was highly dependent on the definition of ULN. Using a tight ULN boundary, re-occurrence of dabigatran-mediated anticoagulation was detected with all doses of idarucizumab except for the supra-therapeutic total dose of 7,5 g. Using a wider ULN boundary, re-occurrence of dabigatran-induced anticoagulation was essentially not observed for idarucizumab doses of 2.5 g or higher.

aPTT: Administration of dabigatran resulted in approximately 2-fold prolongation of mean aPTT coagulation times. Across studies, administration of idarucizumab resulted in a dose-dependent return of

aPTT values to ULN. Thus, reversal of dabigatran-induced effects on aPTT was achieved following idarucizumab administration.

ACT: Administration of dabigatran resulted in approximately 1.5-2 fold prolongation of mean ACT coagulation times. Across studies, administration of idarucizumab resulted in a dose-dependent return of ACT values to ULN. However, the ACT assay appeared to be more variable and the least sensitive of the assays used in the clinical program. Thus, the results of the analyses of the secondary PD biomarkers ETP, TT, aPTT and ACT demonstrate the ability of idarucizumab to reverse the anticoagulant effect of dabigatran. This effect was consistently sustained by administration of a dose of 5 g idarucizumab.

Exploratory bleeding parameters: Three exploratory bleeding parameters were included in the analyses. Fibrinopeptide A (FPA) is a shed blood parameter and data showed that idarucizumab tended to reverse dabigatran-induced reduction of FPA levels, albeit that the CV values were high (>60%). Shed blood volume measurements at baseline were highly variable (0.200 µL – 206 µL, N=34) and therefore no clear effect of dabigatran on shed blood volume could be demonstrated. This parameter was not further explored. In study 1321.1 a washed blood procedure was performed to assess the amount of blood and the bleeding time after incision of the forearm skin with the Surgicut® device. The washed blood parameters optical density AUC, maximum optical density and bleeding time were determined. The inter-subject variability was high with CV values >60% and a clear effect of dabigatran on the washed blood parameters could not be detected.

Concentration-effect relationship: The dTT and the ECT assays were chosen as primary PD biomarkers. Both the dTT and the ECT assays display a linear relationship between plasma dabigatran concentrations and effect over a wide range of concentrations. The ECT assay was not standardized across clinical laboratories and was judged thus to be of limited value in the clinical setting. The dTT correlated most closely with unbound sum dabigatran.

The TT, aPTT and ACT assays were chosen as secondary PD parameters. The TT assay is very sensitive for dabigatran in plasma even at very low dabigatran concentrations and can thus be considered a conservative approach to determine the reversal of dabigatran-induced anticoagulation. However, the TT assay was not standardized across clinical laboratories. The aPTT displays a curvilinear relationship with dabigatran concentrations. Thus, at higher concentrations of dabigatran the aPTT assay levels off and a clear dose-response relationship is lost. Thus, higher aPTT values only indicate significant anticoagulation when induced by dabigatran. However, a reversal of aPTT values to below ULN does indicate reversal of significant anticoagulation. The aPTT assay is readily available in clinical laboratories. The ACT measures the time required for whole blood clotting after activation of the intrinsic coagulation pathway and can be used as a point-of-care test. Although the ACT is widely available and may be performed bedside, it is unclear whether it displays a dose-response relationship with plasma dabigatran.

Interactions: Idarucizumab is a Fab molecule and is thus devoid of the Fc-part and therefore lacks the Fc-mediated effects of monoclonal antibodies. It has no cytokine activity but binds dabigatran potently and specifically. A potential endogenous target for idarucizumab has not been identified and direct interactions with other drugs were considered unlikely. *In vitro* studies have demonstrated no interactions between pro-coagulant drugs such as PCCs, aPCC or rFVIIa and idarucizumab. Moreover, idarucizumab did not inhibit the anticoagulant activity of other anticoagulant drugs such as VKA, FXa inhibitors, heparins or other DTIs of different structure than dabigatran, such as hirudin and argatroban. In an *in vivo* bleeding model where both dabigatran and platelet inhibitors were present in combination, idarucizumab only partially reversed bleeding time. This was likely due to the prolonged bleeding time being a consequence of both thrombin inhibition and platelet inhibition. Thus, a possible target on other drugs to which idarucizumab might bind has not been identified. As such, in the view of the CHMP PK interactions are unlikely to occur. Likewise, PD interactions with other pro-coagulant drugs have not been

demonstrated but the effect of idarucizumab was attenuated when coagulation was inhibited by dabigatran and other anticoagulant drugs in combination. However, due to the specificity of idarucizumab this was expected. It was concluded that there is low likelihood for a drug-drug interaction between idarucizumab and other drugs, except for dabigatran, and for this reason no formal clinical drug-drug interaction (DDI) studies were conducted. This was considered to be consistent with current *Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr.*)*.

Genetic differences in PD response: Gender, age and bodyweight were not significantly correlated with idarucizumab clearance with CrCL. Clearance was approximately 11% lower in Japanese subjects than for non-Japanese. No other significant covariate effects were observed. Pre-specified pharmacogenomics analyses were not performed as genetic variations that may explain or predict individual response to idarucizumab have not been identified. However, DNA banking samples are collected in the ongoing study 1321.3. These will be stored by the applicant for up to 15 years and may be analysed at a later time to identify potential genetic factors that could influence therapeutic outcome or adverse reactions. This was endorsed.

PK-PD results: Linear and nonlinear (Emax) mixed effects models were used to examine the PK/PD relationship of dabigatran analyte concentration and ECT, dTT, TT, and aPTT and to identify key covariates influencing these relationships. The PK/PD model was conditioned on unbound sum dabigatran (observed and PK-model predicted) and on the PK-model derived idarucizumab-free sum dabigatran. The relationships between dabigatran species and ECT and dTT could be described by slope-intercept (linear) models. The structural models are consistent with previous experience on the relationship between dabigatran species and ECT (linear), aPTT (Emax) and TT (Emax). Inter-individual and residual variability were moderate throughout the models, the estimates were generally sufficiently precise. Covariates tested for the dabigatran concentration-biomarker response relationships included pre/post-idarucizumab measurement of biomarkers (PREFAB2), sex, age, body weight, and race. Because one of the three studies (1321.5) included only Japanese subjects potential confounding of race and study was also explored. Since the subgroup of females was small, covariate analysis may be biased in this point. Age, body weight, and measurement prior to idarucizumab administration were found to be significant predictors for selected coagulation markers, with relative differences of ≤7.1% for a 10 year deviation from median age, 10 kg deviation from median weight, or for measurement pre- versus post-idarucizumab administration. As a result of the alternative analysis where the effect of race is replaced with study as a covariate, significant study effects were found for the relationships between concentration and ECT (Study 1321.1), aPTT (Study 1321.2), and TT (Study 1321.1). For the aPTT models, the inclusion of the study effect rendered the previously included covariate effect of age insignificant. Sex was not a significant factor on coagulation time.

The best fit between observed and model predicted values was seen for the models of observed unbound sum dabigatran – ECT and the observed unbound sum dabigatran- dTT relationship. VPC plots indicated a less good fit of the predicted dabigatran analytes (e.g. predicted unbound sum dabigatran, predicted idarucizumab free dabigatran IFSD) - coagulation parameter relationship than the one for the observed unbound sum dabigatran – coagulation analyt models. This holds also true for the QQ plots for ECT and dTT, which suggest severe deviation from normal distribution. In addition, simulation of IFSD after one 5g idarucizumab dose for an average Caucasian with impaired renal function on the basis of the PopPK model indicated an extremely high variability. Cmax values ranged between 0.5 and 60 ng/mL.

Simulations: The population PK and PK/PD models were used to simulate coagulation profiles and reversal rates under a number of dose and regimen scenarios. The simulations suggest that at idarucizumab doses ≥ 2g all patients experience a reversal of the dabigatran anti-coagulating effect below values of ULN, as measured by ECT and dTT. With increasing idarucizumab dose this reversal lasts longer. At the 5g and 2x 2.5g dose regimen, only a small percentage of subjects (around 5%) were expected to achieve

coagulation values above ULN within 28 hours post dosing at all. In contrast, at 2 g idarucizumab in 50% of typical Caucasian subjects with normal renal function ECT values around the 110% ULN would already be expected within 8 hours post dosing. These data supported the proposed clinical dose. However, the uncertainty for an individual prediction was in the low dose range very high.

The simulation further suggested that renal impairment did not have a major impact on the dose-effect relationship, despite its influence on idarucizumab as well as on dabigatran PK. The Applicant provided an explanation: clearance of both idarucizumab and dabigatran is reduced with renal impairment. While renal impairment increases dabigatran body load it also slows elimination of idarucizumab, increasing the opportunity for binding and decreasing the amount of idarucizumab eliminated unbound.

Simulations based on the model derived from the RE-LY dabigatran study showed somewhat different values. This was due to a difference in the estimates of the clearance function. IFSD was predicted to be higher and subsequently higher maximum values above ULN of the coagulation assays were reached. Nevertheless, with both models ≥ 2g idarucizumab is predicted to result in 100% reversal, and time of reversal is nearly unchanged. Furthermore, albeit the discrepancy in clearance was more prominent in more severe renal impairment (CrCL of 40 ml/min), the differences in simulated coagulation effects were minimal (at 2.5g + 2.5 g; Median dTT of 32.9 vs 32.1s; Median ECT of 39.5 vs 37.4s).

2.4.4. Discussion on clinical pharmacology

Idarucizumab is a humanised antibody fragment (Fab) molecule designed to reverse the anticoagulant effect of dabigatran. It is administered intravenously. Dabigatran is a direct thrombin inhibitor, an anticoagulant that is the active principle of the prodrug, DE. Idarucizumab binds to dabigatran with an affinity (KD) of 2.1 pM, which is ~300-fold more potent than the binding affinity of dabigatran for thrombin. The process by which the complex is formed with dabigatran is essentially irreversible.

A validated ELISA method was used to measure total idarucizumab in plasma and urine. At the time of the assessment of current application there was no quantitative assay to measure free idarucizumab available. An immunoassay method was considered not feasible in the presence of dabigatran.

A three-tiered approach was used for anti-drug antibody (ADA) detection. For screening and confirmation a **drug-bridging electrochemiluminescence (ECL) method** was applied. It was noted that only ADA concentrations ≥ 250 ng/mL would be detected. Selectivity was not confirmed in samples spiked with plasma from renally impaired patients. Therefore, cut point will be further investigated in renal impairment human plasma samples. Furthermore, a hook effect was detected at positive control concentrations > 8000 ng/mL. Nevertheless, those samples were still positive above cut point. In general, the assay was considered sufficiently validated. **Epitope specificity assessments** were performed on study samples that were confirmed positive for ADA in the method described above. Epitope specificity was assessed using a competitive format of the ECL method described above (analogous to the confirmatory assay) in which molecules related to idarucizumab were evaluated for their potential to block the ADA signal in the ECL method. The neutralising anti-idarucizumab antibody assay (**Nab assay**) was not considered sufficiently validated. The applicant pointed out a high false positive rate and the unknown reason for it. The applicant further argued that assuming worst case of the highest ADA titer measured so far in a neutralising ADA (nADA) positive control sample, the ratio of idarucizumab to nADA would still be 500:1. The CHMP agreed that it is unlikely, that nADA could affect efficacy severely.

The clinical pharmacology of idarucizumab has been well described in **283 healthy volunteers** investigated in three Phase I trials. A Phase III study (study 1321.3) in patients was ongoing at the time of the assessment of the current application (the second interim analysis of the RE-VERSE AD trial assessed within current application included clinical data from 123 patients recruited into RE-VERSE AD

up to Apr 01, 2015 and central laboratory data for assessment of efficacy were available for 90 patients). The PK data set from **90 patients** which was available indicated no relevant differences between the plasma PK profiles of patients and phase I volunteers when renal function was considered. Population PK analysis was performed so far with the PK data of the Phase I healthy volunteers. Estimation of the PK parameters and covariate analysis in patients was missing for the target patient population. Therefore, the MAA agreed to perform such an analysis after completion of study 1321.3 in order to fully analyse and describe the PK of idarucizumab in patients. Since robustness and fit of the current PK model was considered only moderate the applicant intended to perform future analysis to explore alternative binding models (between idarucizumab and dabigatran) while incorporating data from ongoing study in patients.

The current population PK-PD idarucizumab-dabigatran binding model also has limitations with regard to severe renal impairment. The ongoing Phase III study is likely to recruit additional patients with severe renal impairment. Hence, more data should be available in the future. The model assessed within current application predicted that in patients with renal impairment, increasing exposures of dabigatran will be accompanied by increasing exposures of idarucizumab. Further, for a patient with a CrCL of 40 mL/min, it was predicted that the relative idarucizumab exposure increase will be higher than the dabigatran exposure increase when compared to a subject with a CrCL of 90 mL/min. From the perspective of ensuring sufficient idarucizumab exposure to bind dabigatran, this was considered reassuring by the CHMP. Still it is known that in patients with severe renal impairment, the plasma concentration of dabigatran could be 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal impairment. On the other hand, estimations based on the actual data of n=68 patients/volunteers reveal that exposure in severely impaired patients was increased about 3-fold. Therefore, some uncertainty remained whether idarucizumab exposure with the originally proposed posology would be sufficient in patients with severe renal impairment. In the ongoing Phase III study, a slightly lower proportion of patients with severe renal impairment achieved complete reversal based on ECT and dTT compared to patients with no or mild-moderate renal impairment. This was a noteworthy finding, although it could be due to chance or other factors.

The information available so far did not allow defining a differentiated posology based on renal function. The recommendations regarding retreatment with idarucizumab if bleeding reappears were included in the SmPC. This was considered to mitigate to a certain degree the risk in case of underexposure of idarucizumab in patients with severe renal impairment.

Based on these considerations, the posology of 5 g (2 vials of 2.5 g) with the possibility of retreatment was considered acceptable.

2.4.5. Conclusions on clinical pharmacology

Simulations using the population PK and PK/PD models suggested that the proposed total dose of 5 grams given as two 2.5 gram infusions separated by 15 minutes resulted in complete reversal in Caucasian or Japanese patients across a wide range of renal function and dabigatran exposure. However, estimation of the PK parameters and covariate analysis was missing for the target patient population. Therefore, the applicant agreed to perform such an analysis after completion of study 1321.3 in order to fully analyse and describe the PK of idarucizumab in patients. Since robustness and fit of the current model was considered only moderate, the applicant agreed to perform future analysis to explore alternative binding models (between idarucizumab and dabigatran) while incorporating data from ongoing studies in patients.

Furthermore, some uncertainty remained whether idarucizumab exposure with the proposed posology will be sufficient in severe renal impairment. In the ongoing Phase III study, a slightly lower proportion of patients with severe renal impairment achieved complete reversal based on results of ECT and dTT

compared to patients without or with mild to moderate renal impairment. It was agreed to re-assess it after completion of the study 1321.3. The recommendations included in the SmPC regarding retreatment with idarucizumab if bleeding reappears should to some extent mitigate the risk in case of underexposure of idarucizumab in severe renal impairment. Based on these considerations, the posology of 5 g (2 x 2.5 g) with the possibility of retreatment was considered acceptable by the CHMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

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. As clinical outcome data were not used for the dose estimation, further discussion regarding dose response can be found in the pharmacology part of the AR.

2.5.2. Main studies

This clinical development program is focused on demonstrating pharmacologic reversal of the anticoagulant effect of dabigatran. In case of emergency surgery in dabigatran patients or in the rare cases of life-threatening or uncontrolled bleeding associated with dabigatran, there is a potential clinical need for such an agent.

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; RE-VERSE AD). The second interim analysis of RE-VERSE AD was included with the responses to the Day 120 LoQ in the current application. It contained available efficacy data for the ongoing RE-VERSE AD trial. It included clinical data from 123 patients recruited into RE-VERSE AD up to April 01, 2015 and central laboratory data for assessment of efficacy that were available for 90 patients. The report included the 26 patients reported in the interim Clinical Trial Report submitted at the initial submission of the current application and the 90 patients as reported in NEJM on Jun 22, 2015.

Phase I studies (1321.1, 1321.2 and 1321.5)

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 (REVERSE AD; 1321.3).

All 3 Phase I studies in the idarucizumab program comprised only healthy volunteers. Studies 1321.1 and 1321.5 comprised only male subjects while study 1321.2 included also female volunteers. Subjects with renal impairment participated only in 1321.2. Both studies 1321.1 and 1321.2 were conducted in Belgium (majority: white subjects) whereas study 1321.5 included Japanese subjects. A short summary of the inclusion criteria is provided in Table 1.7.1: 1.

There were a total of 283 volunteers in these studies, with 224 receiving at least one dose of idarucizumab. Thus, by combining safety with dose-response and “proof of concept”, Phases I and II were accomplished in a single step.

Table 1.7.1: 1 Inclusion criteria for the Phase I studies 1321.1, 1321.2, and 1321.5

	1321.1	1321.2	1321.5
Sex	Male	Male and female	Male
Age [years]	18 to 45	≥45 to ≤64 (healthy) ≥65 to ≤80 (elderly) ≥45 to ≤80 (renal impairment)	≥20 and ≤45
BMI [kg/m^2]	18.5 to 29.9	≥18.5 to ≤29.9 (healthy) ≥18.5 to ≤32 (elderly and renal impairment)	≥18.5 to <25.0
Renal impairment	No	No impairment, mild (CrCl of ≥60 to <90 mL/min), and moderate impairment[1] (CrCl ≥30 to <60 mL/min)	No

[1] According to Cockcroft & Gault

Source data: [c02093109, Section 9.3.1 ; c02742738, Section 9.3.2 ; c03026940, Section 9.3.2]

Treatments

The vast majority of subjects received idarucizumab as single dose infusion (79.5%), see Table 3.1.1: 2. 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.

Table 3.1.1: 2 Exposure to idarucizumab by dose for studies 1321.1, 1321.2, and 1321.5 – subjects pretreated with DE

Total idarucizumab dose	DE+placebo N (%)	DE+Ida N (%)
Treated subjects	70 (100)	117 (100)
Dosage		
Single dose (20 mg to 8 g)		93 (79.5)
Two separate infusions 15 min apart (2.5 g+2.5 g)		9 (7.7)
Two separate infusions 60 min apart (5 g+2.5 g)		9 (7.7)
Single infusion 2.5g+2.5g re-exposure after 60 days		6 (5.1)

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

Source data: [c03076696, Table 1.1.2.2]

Outcomes / endpoints

Efficacy variables assessed in the combined analysis of Phase I trials

The efficacy of idarucizumab was evaluated using measurements from the biomarkers, dTT, ECT, TT and aPTT, with the primary evaluation focusing on either ECT or dTT. Evaluations using TT and aPTT were considered as secondary analyses. Additionally, measurements of the unbound sum dabigatran were summarized to provide additional evidence supporting the efficacy of idarucizumab.

Reversal (%): for each individual subject pre-treated with dabigatran the reversal was defined as below:

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

- The ULN value was calculated as “mean+2*SD” using data from studies 1321.1 and 1321.2. The pre-dose values were measurements taken prior to the administration of idarucizumab/placebo, post-dose values were measurements taken post the administration of idarucizumab/placebo. The reversal defined as above using the 100% ULN was analysed as sensitivity analyses. The computed reversal was truncated at 100% if it was >100%, to 0% if it was <0%. A negative reversal would be obtained if the pre-dose value was smaller than the post-dose value, such as for a subject given placebo, instead of idarucizumab, after the pre-treatment with dabigatran.
- Achievement of complete reversal within 4 hours since the start of the administration of idarucizumab or placebo (calculated reversal ≥100%) (Yes/No)
- Achievement of 80% of reversal within 4 hours since the start of the administration of idarucizumab or placebo (Yes/No)
- Duration of complete reversal for subjects that achieved complete reversal within the first four hours since the start of the administration of idarucizumab or placebo.
- Time to complete reversal for subjects that achieved complete reversal within the first four hours since the start of the administration of idarucizumab or placebo
- Change from pre-dose bio-marker measurements at each time point

The chosen efficacy endpoints are regarded as appropriate and will allow assessing the potential of idarucizumab to reverse the pharmacological effect of dabigatran etexilate.

Sample size

Study 1321.1: Initially it was planned to include a total of 140 subjects (8-12 per dose group). Later on additional dose groups were included into the study and the sample size was increased to 157 subjects.

Study 1321.2: Forty six subjects (high dose: 26, medium dose: 6, low dose: 14) were planned to be included into the study.

Study 1321.5: It was planned to include a total of 80 subjects (8-12 per dose group). The sample size in none of the phase I trials was based on statistical considerations.

Randomisation

Studies 1321.1 & 1321.5: Within each dose, subjects were randomized in a 3:1 ratio (idarucizumab: placebo).

Study 1321.2: Block randomisation was used to randomise subjects in a 1:1 ratio to one of the 2 treatment sequences: idarucizumab followed by placebo and vice versa. Block size was 8 subjects for the low and high dose/elderly group (65-80 y) respectively while for all other treatment groups a block size of 6 was used.

Blinding (masking)

Studies 1321.1 & 1321.5: Both studies were (double) blinded regarding treatment but unblinded regarding dose level. 1321.2: The study was blind except the re-exposure to idarucizumab in subjects aged 45 to 64 years that was open label.

Statistical methods

All subjects that were pre-treated with dabigatran etexilate and had post idarucizumab/placebo biomarker measurements were included in the evaluation of the efficacy endpoints. In each of study all parameters were described by statistical characteristics (continuous data: number of observations, mean, median, percentiles; categorical data: relative and absolute frequencies). Wilson’s score method was used to calculate the 95% confidence limits for the proportion of subjects achieving complete, 80% or 50% of reversal (reversal defined as a reduction of elevated coagulation times just before idarucizumab infusion to the normal range after idarucizumab treatment). No statistical hypotheses were tested.

Summary of results of individual phase I studies

The following subsections describe the key pharmacodynamics results of the Phase I studies. The terms used to describe mean coagulation data for reversal of dabigatran-induced anticoagulation per dose group across individual Phase I trials is provided in Table 2.1: 1

Table 2.1: 1 Definition of terms used to describe mean data for reversal of dabigatran-induced anticoagulation

Term	Definition
'immediate'	Timing of the reversal. Reversal of dabigatran induced anti-coagulation occurred directly at the end of idarucizumab infusion
'complete'	Magnitude of the reversal. Return of the mean coagulation time of a specific dose group to below the respective ULN
'sustained'	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.

Trial 1321.1

(Randomised, double-blind, placebo-controlled Phase I study in healthy male volunteers to investigate safety, tolerability and pharmacokinetics of single rising doses of idarucizumab (Part 1) and to explore the dose of idarucizumab effective to reverse dabigatran anticoagulant activity (Part 2)

Objectives

Parts 1 to 3: To investigate the safety, tolerability, and pharmacokinetics of single rising intravenous doses of idarucizumab (20 mg to 8 g)

Parts 2 and 3: To explore the effect of different doses of idarucizumab to reverse dabigatran anticoagulant activity in subjects pre-treated with dabigatran etexilate

Methods

An overview of the study design and dosing in Study 1321.1 is provided in Table 2.1.1: 1.

Table 2.1.1: 1 Overview of study design and dosing in Study 1321.1

Study design	Study Part	Idarucizumab dose i.v.	DE pre-dosing	Ida:placebo
Randomised, double-blind, placebo-controlled within dose groups, single centre, single dose (Part 3: 2 infusions)	Part 1 (N=110)	20 mg to 8 g (1h inf., 10 steps) 1, 2, 4 g (5 min inf.)	n.a. n.a.	6:2 6:2
	Part 2 (N=35)	1, 2, 4 g (5 min inf.)	220 mg bid	9:3
	Part 3 (N=12)	5 g + 2.5 g (60 min later, 5 min inf.)	220 mg bid	9:3

inf., infusion; i.v., intravenously; n.a., not administered

Disposition of subjects

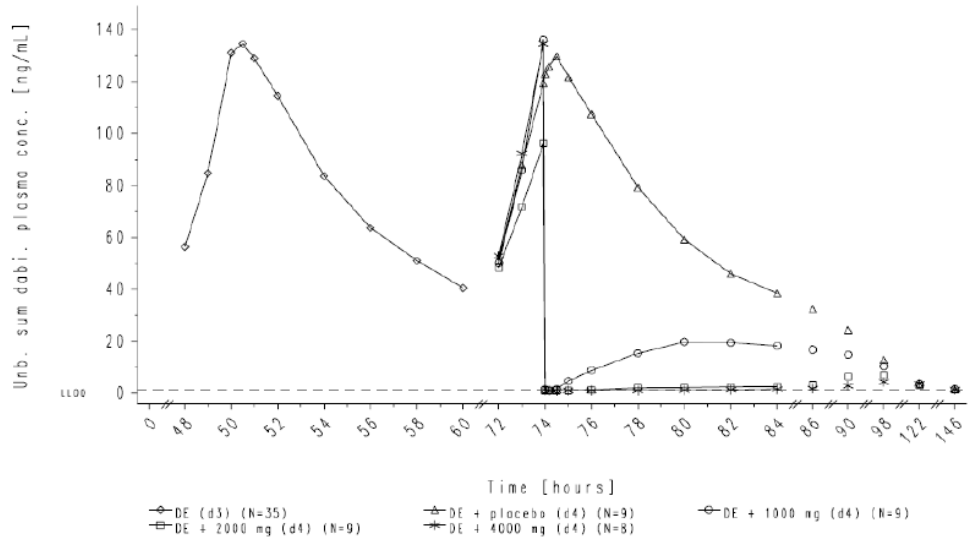
A total of 157 healthy male subjects (110 subjects in Part 1, 35 subjects in Part 2 and 12 subjects in Part 3) were entered into this trial at a single centre. The first subject in this trial was enrolled on 20 Sep 2012 and the last subject left the trial on 29 Nov 2013.

Serial blood samples for determination of coagulation time measurements dTT, ECT, aPTT and TT were taken pre-dose and 15 min post dose (Part 1: 8 g 1 h infusion and 4 g 5 min infusion, only) and over up to 72 hours (Part 2 and 3) following administration of DE or DE+idarucizumab. An upper limit of normal (ULN) was determined for each coagulation time assay based on the mean + 2*SD of all available pre-dose measurements.

Results

Effect of idarucizumab on dabigatran pharmacokinetics

In Part 2 and 3, median peak (at 2 h post-dose) sum dabigatran concentrations at steady state were comparable with the median exposure previously observed in patients with atrial fibrillation after 150 mg DE twice daily dosing. Immediately after the end of infusion of all idarucizumab doses, unbound sum dabigatran plasma concentrations dropped to or below the lower limit of quantification (1 ng/mL), concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The effect of idarucizumab on unbound sum dabigatran concentrations was dose-dependent, whereby gMean concentrations of unbound sum dabigatran remained below 20 ng/mL after infusion of 1 g idarucizumab, below 10 ng/mL after infusion of 2 g idarucizumab and below 5 ng/mL after infusion of higher idarucizumab doses over the entire observation period of 72 hours (Part 2 results are exemplified in Figure 2.1.1: 1).



LLOQ=1 ng/mL; BLQ values replaced by LLOQ during re-distribution phase
Source data: c02093109, Figure 15.6.5.3.13: 11

Figure 2.1.1: 1 Geometric mean plasma concentration-time profiles of unbound sum dabigatran after multiple oral administration of 220 mg DE bid with and without single iv infusion of 1 g to 4 g idarucizumab or placebo over 5 min (linear scale)

Table 2: gMean concentrations of unbound sum dabigatran in plasma after 1.92 to 12 h, at steady state of dabigatran, on Day 4

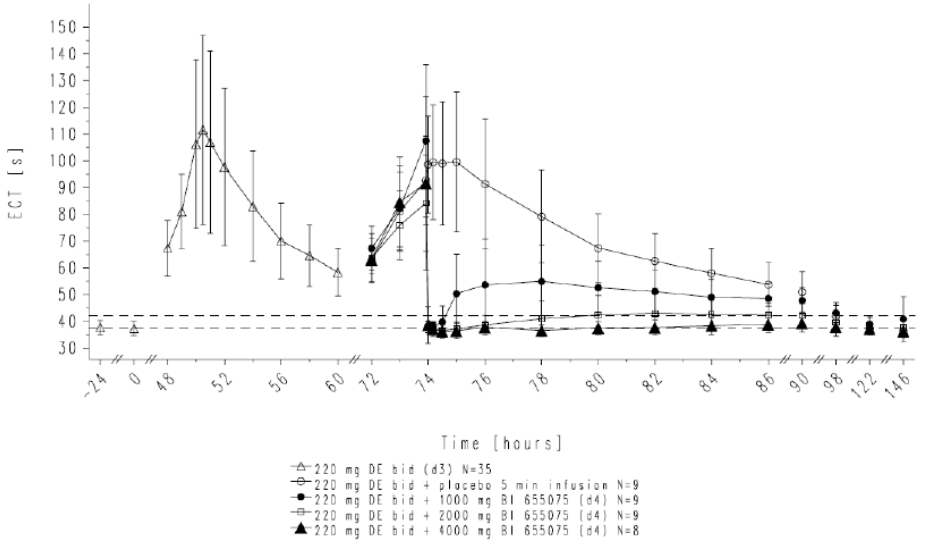
Dose group	$C_{1.92,ss}$ [ng/mL]	$C_{2,ss}$ [ng/mL]	$C_{2.5,ss}$ [ng/mL]	$C_{6,ss}$ [ng/mL]	$C_{12,ss}$ [ng/mL]
Part 2 *(5 min infusion)*					
DE+plc	119	123	130	79.2	38.5
DE+1 g Ida	136	1.59	NC	15.3	18.2
DE+2 g Ida	96.2	NC	NC	NC	NC
DE+4 g Ida	135	NC	NC	NC	NC
Part 3 *(5 min infusion)*					
DE+2 doses plc	101	95.6	92.9	54.8	28.9
DE+5 g+2.5 g Ida	112	NC	NC	NC	NC

Plc=placebo, Ida=idarucizumab, NC = not calculated when more than one third of individual values within a treatment group were below the lower limit of quantification

Pharmacodynamics

Idarucizumab infusion of 8 g over 1 h (dose group 10) and 4 g over 5 min (dose group 13) in the absence of dabigatran had no apparent effect on the coagulation parameters dTT, ECT, aPTT and TT when determined 15 min after end of the infusion. Infusions of idarucizumab at these doses had no apparent effect on the endogenous thrombin generation potential (ETP). DE administration consistently prolonged coagulation times of all coagulation parameters in the absence of idarucizumab. 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 (i.e. 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
- 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



- - - - Mean baseline = 37.295 s, normal upper reference limit = 42.101 s
Source: [c02093109, Figure 15.7.5.3: 3]

Figure 2.1.1: 2 Mean effect time profiles (+/-SD) of ECT at dabigatran steady state after infusion of 1 g, 2 g, or 4 g idarucizumab or placebo 5 min on Day 4. Start of idarucizumab infusion was at planned time 73:55.

The reversal of dabigatran anticoagulation was also evidenced by a dose-dependent reduction of the ratio between the mean area under the effect curve (AUECabove,2-12) after idarucizumab infusion on Day 4 and before idarucizumab infusion on Day 3 (Table 2.1.1: 2).

Table 2.1.1: 2 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.
Source: [c02093109, Table 11.5.3.3: 2]

The data presented show that administration of idarucizumab alone has no effect on the measured clotting parameters. The anticoagulative effect of dabigatran was reversed in a time and dose dependent manner.

Doses >2g reversed the dabigatran effect completely and for a time period of at least 72h.

Trial 1321.2

Title: Randomised, double-blind, placebo-controlled, two-way crossover Phase Ib study to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 655075 and to establish the efficacy of BI 655075 in reversal of dabigatran anticoagulant activity in volunteers

Objectives

To investigate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of idarucizumab 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. Objectives of the study are appropriate to compare the effect of idarucizumab administration after dabigatran intake versus placebo/dabigatran. All participants received in a cross over design both placebo and idarucizumab.

Methods

Trial 1321.2 assessed the neutralizing effect of idarucizumab on dabigatran-induced anticoagulation in male and female healthy volunteers (age 45-64 years and 65-80 years) and subjects with mild or moderate renal impairment. Idarucizumab doses tested included a subtherapeutic dose (1 g) as well as a medium (2.5 g; approximately equimolar dose) and the target therapeutic dose (5 g), either given as single infusion or split into 2 intravenous infusions of 2.5 g 60 min apart (see Table 2.1.2: 1).

Table 2.1.2: 1 Study population and doses of DE and idarucizumab in study 1321.2

Study population (N-size) [M:F ~ 1:1]	DE dose (mg; bid)	Idarucizumab dose (g)	Other aspects
Healthy, 45-64 years (6)	220	2.5	re-dosing DE and idarucizumab
Healthy, 45-64 years (6)	220	5	re-dosing DE
Healthy elderly, 65-80 years (8)	220	1	
Healthy elderly, 65-80 years (8)	220	5	
Mild renally impaired, 45-80 years (6)	150	1	
Mild renally impaired, 45-80 years (6)	150	5	
Moderate renally impaired, 45-80 years (6)	150	2.5 + 2.5 (one hour apart)	

DE = dabigatran etexilate, M=male, F=female

A total of 46 volunteers participate in the trial:

- 12 healthy subjects (6 female and 6 male) aged 45 to 64 years (receiving either 2.5 or 5 g idarucizumab)
- 16 healthy elderly subjects (at least 12 subjects, 6 female and 6 male) aged 65 to 80 years (receiving either 1 g or 5 g idarucizumab)
- 12 subjects (at least 4 of each sex) aged 45 to 80 years with mild renal impairment (creatinine clearance ≥60 to <90 mL/min) receiving either 1 g or 5 g idarucizumab. Of these, at least 50% had to have a creatinine clearance <75 mL/min
- 6 subjects (at least 2 of each sex) aged 45 to 80 years with moderate renal impairment (creatinine clearance ≥30 to <60 mL/min) receiving 2 x 2.5 g idarucizumab
- Healthy subjects aged 45 to 64 years underwent re-exposure with idarucizumab in Period 3 (4 days of treatment with DE, idarucizumab on Day 4), 2 months after completing Period 2.

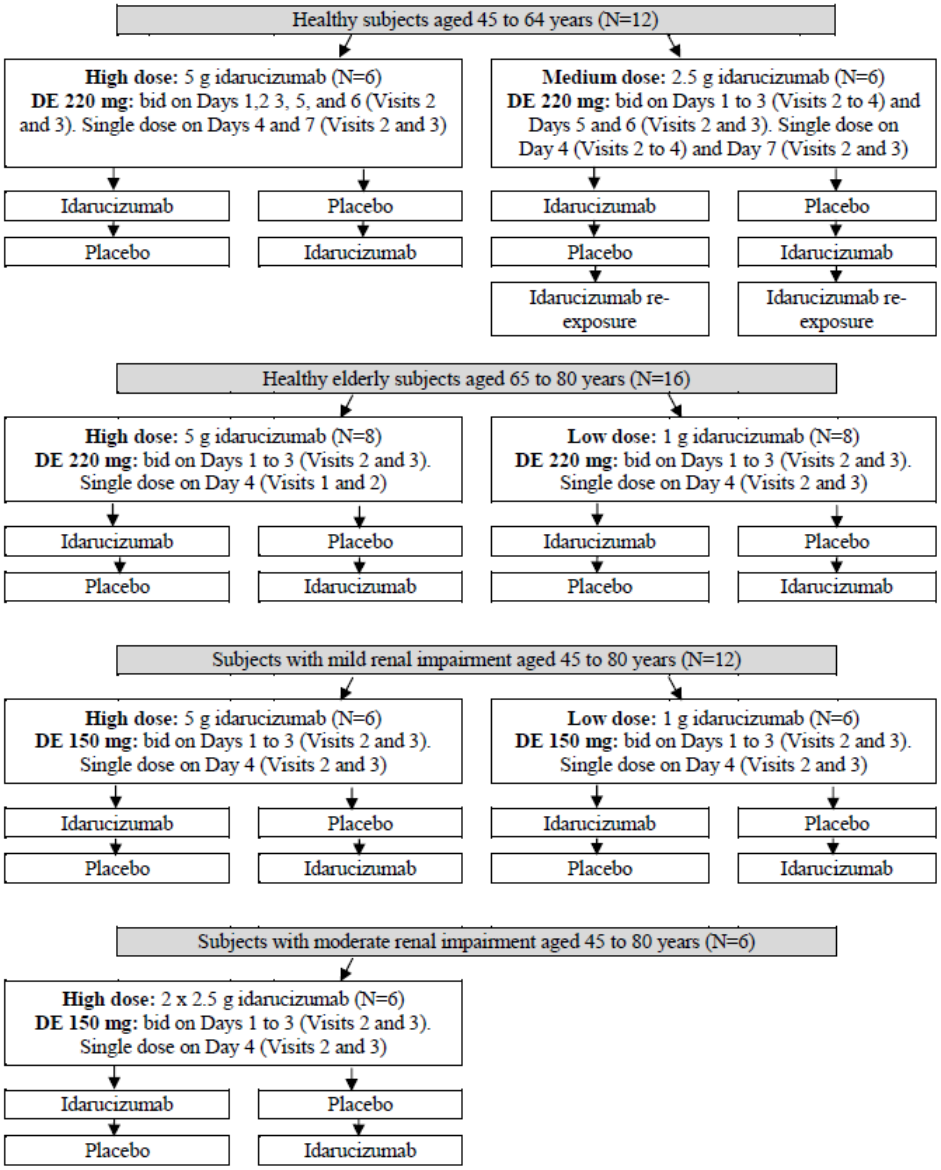


Figure 9.1: 1 Overview on treatment groups and doses of study medication

The chosen population for this trial tried to better reflect the proposed population for idarucizumab. Included were elderly subjects otherwise healthy and subjects with mild and moderate renal impairment. The assessment of idarucizumab effect in this population was regarded as very important in addition to the phase III patient study still ongoing and provided supportive data.

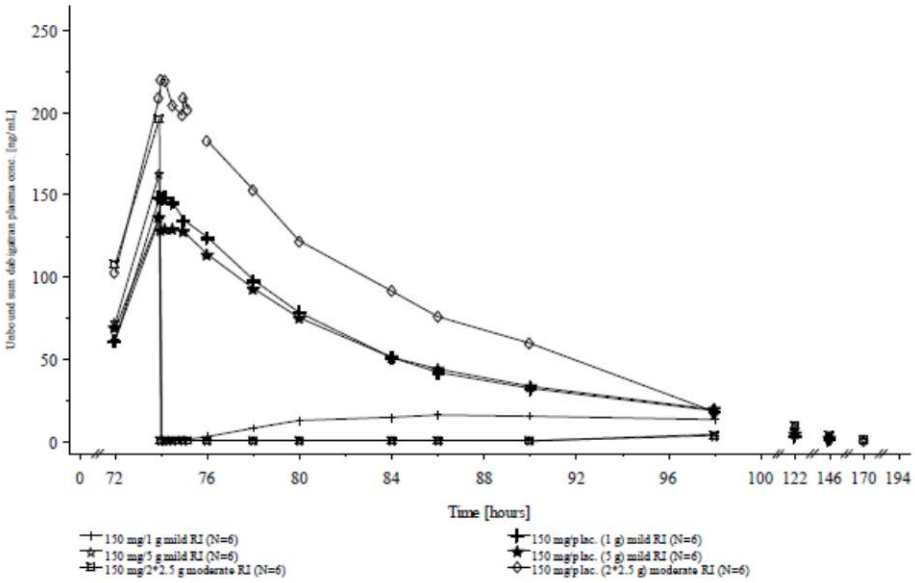
- **Endpoints**

The primary PD endpoint was reversal of dabigatran-induced prolongation of blood coagulation times. For this purpose, anticoagulation tests with primary focus on ECT and dTT were used; aPTT and TT were supportive secondary readouts. ULN values were determined for each coagulation time assay as a back-calculated value corresponding to 20 ng/mL unbound sum dabigatran based on a PK/PD correlation between unbound sum dabigatran and the respective clotting assay (primary) and the mean + 2*SD (secondary) of all available pre-dose measurements from 1321.1 and 1321.2

Pharmacokinetic results

Effect of idarucizumab on dabigatran exposure

Median sum dabigatran 2 h concentrations as determined in the absence of idarucizumab were comparable or slightly higher compared with the median 2 h exposure achieved in the RE-LY trial (U09-3249-02) after 150 mg DE twice daily dosing in patients with atrial fibrillation. After the end of infusion of all idarucizumab doses and in all populations unbound sum dabigatran plasma concentrations dropped to or below the lower limit of quantification of 1 ng/mL (Figure 2.1.2: 1 depicts results from subjects with renal impairment), 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.



Source data: [c02742738, Figure 15.6.5.3.3: 29]

Figure 2.1.2: 1 Geometric mean concentration time profiles of unbound sum dabigatran after 150 mg DE bid dosing and infusion of 1 g, 5 g, or 2x2.5 g idarucizumab or matching placebo (linear scale)

Pharmacodynamic results

Effect of idarucizumab infusion on the anticoagulant effect of dabigatran, effect of age and renal impairment

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. These results were further supported by the dose-dependent reduction of coagulation marker AUEC2-12 by up to 99% compared to placebo treatment. The reversal effect of idarucizumab was similar in male and female subjects.

Table 1: Reversal[1] of dabigatran-induced clotting time prolongation – PDS

	Reversal[1] determined based on	
Treatment group	dTT	ECT
Healthy subjects aged 45 to 64 years		
2.5g Ida (45-64y)	Complete, up to 24 h[2]	Complete, up to 24 h[2]
2.5g Ida (45-64y) re-exposure	Complete, up to 4 h	Complete up to 24 h
5g Ida (45-64y)	Complete, up to 24 h[2]	Complete, up to 24 h[2]
Healthy elderly subjects aged 65 to 80 years		
1g Ida elderly	Complete, up to 1 h	Complete, up to 1 h
5g Ida elderly	Complete + sustained	Complete + sustained
Subjects with mild renal impairment aged 45 to 80 years		
1g Ida mild	Complete, up to 2 h	Complete, up to 2 h
5g Ida mild	Complete + sustained	Complete + sustained
Subjects with moderate renal impairment aged 45 to 80 years		
2x2.5g Ida mild	Complete + sustained	Complete + sustained

[1] Return of the mean coagulation time of a specific dose group to baseline (i.e. the respective clotting time corresponding to 20 ng/mL unbound sum dabigatran as determined by PK/PD correlation)
[2] DE redosing at 24 h after idarucizumab infusion

All subjects treated with idarucizumab showed reversal of the dabigatran-induced prolongation of clotting time and none of the subjects (0%) receiving placebo showed reversal. Sustained reversal over the complete observation period depended on the dose: infusion of 2.5g and 5g idarucizumab resulted in sustained reversal of dabigatran-induced clotting time prolongation over the observation period of at least 24 h. No influence of sex, age, or renal impairment was shown.

Additional testing:

Re-exposure to idarucizumab
When a second dose of 2.5 g idarucizumab was administered approximately 2 months after the first 2.5 g dose to healthy volunteers aged 45 to 64 years, 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.

Re-dosing of dabigatran etexilate (DE)
Healthy subjects aged 45 to 64 years dosed with either 2.5 or 5 g idarucizumab (or placebo) received 5 doses of 220 mg DE bid starting 24 h after the end of idarucizumab infusion. DE pre-treatment, and re-start of DE treatment 24 h after placebo or idarucizumab administration resulted in similar trough and 2 h post-dose unbound sum dabigatran concentrations as well as dTT, ECT, aPTT, and TT ratios to baseline. This suggests that normal DE treatment can be reinstituted 24 hours after idarucizumab administration.

The applicant provided data in a limited number of 6 healthy subjects to investigate the possibility of re-treatment with idarucizumab in a possible emergency situation. These data were regarded as very important. Although the number of cases was rather limited, data showed that re-exposure to idarucizumab resulted in comparable reversal of DE effect compared to the first exposure. Pre-treatment with DE and restart of DE treatment 24 h after infusion of placebo or idarucizumab to 12 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. The conclusion that DE treatment can be reinstituted 24 h after the last dose of idarucizumab was agreed. Administration of another antithrombotic agent could be done at any time as idarucizumab is specific for dabigatran.

Trial 1321.5

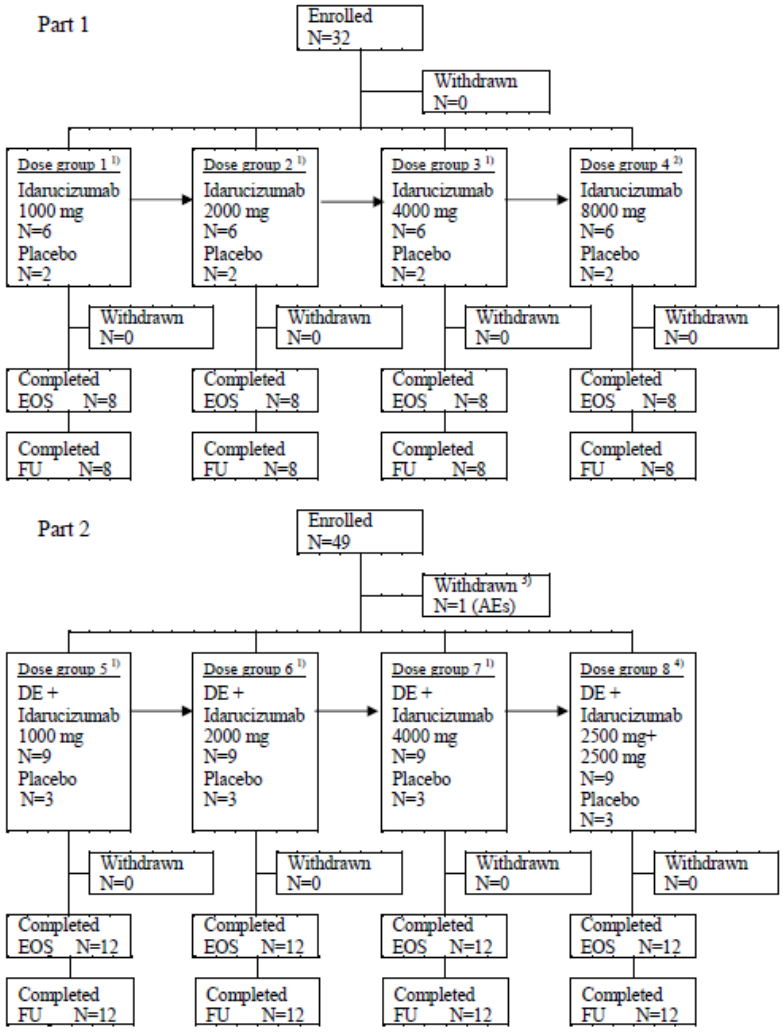
Title: Randomised, double-blind within dose groups, placebo-controlled Phase I trial in healthy Japanese male volunteers to investigate safety, tolerability and pharmacokinetics of different doses of idarucizumab (part 1) and to explore the effective dose of idarucizumab to reverse dabigatran anticoagulant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

Objectives

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

Methods

In this randomised, double-blind within dose-groups, placebo-controlled, single center study, single doses of idarucizumab and multiple doses of dabigatran etexilate (Part 2, only) were administered to 80 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. Within each dose-group, the assignment of active treatment: placebo was 6:2 (Part 1) or 9:3 (Part 2).



Abbreviations: EOS=end of study; FU=follow-up; AEs=adverse events; DE=dabigatran etexilate
[1] infusion time=5 min; [2] infusion time=1 h; [3] in "dabigatran period"; [4] infusion time=5 min + 5 min with an interval of 15 min
Source data: Tables 15.1.1: 1 to 15.1.1: 4

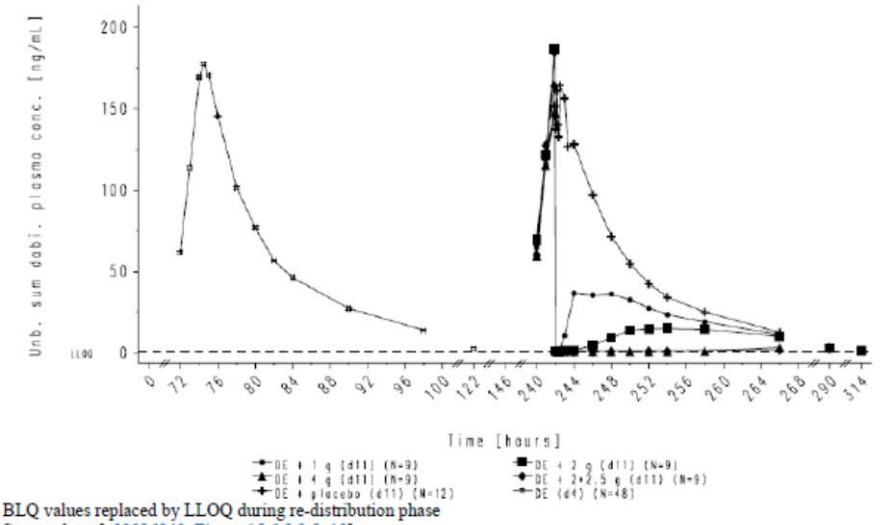
Figure 10.1: 1 Disposition of subjects

Serial blood samples for determination of the coagulation markers dTT, ECT, aPTT and TT were taken up to 72 hours after DE or idarucizumab administration. The ULN was determined for each coagulation assay based on the mean+2*SD of all available pre-dose measurements.

Results

Effect of idarucizumab on dabigatran pharmacokinetics

Median 2 h post-dose sum dabigatran concentrations at steady state were slightly higher compared with the median exposure previously observed in patients with atrial fibrillation after 150 mg DE twice daily dosing. During idarucizumab infusion, a rapid and substantial decline of unbound sum dabigatran concentrations to at least the LLOQ (1 ng/mL) was observed, concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The duration of the effect of idarucizumab on unbound sum dabigatran concentrations increased with dose (Figure 2.1.3: 1), 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.



BLQ values replaced by LLOQ during re-distribution phase
Source data: [c03026940, Figure 15.6.5.3.5: 13]

Figure 2.1.3: 1 Geometric mean unbound sum dabigatran plasma concentration-time profiles after multiple administration of 220 mg DE bid and idarucizumab (total doses of 1 g to 5 g) or placebo (linear scale)

Pharmacodynamics

Part 1: Idarucizumab infusion of 8 g over 1 h and 4 g over 5 min in the absence of dabigatran had no apparent effect on the coagulation parameter dTT, ECT, aPTT and TT when determined 15 min after end of the infusion.

Part 2: DE administration consistently prolonged clotting times of all clotting parameters in the absence of idarucizumab. Administration of:

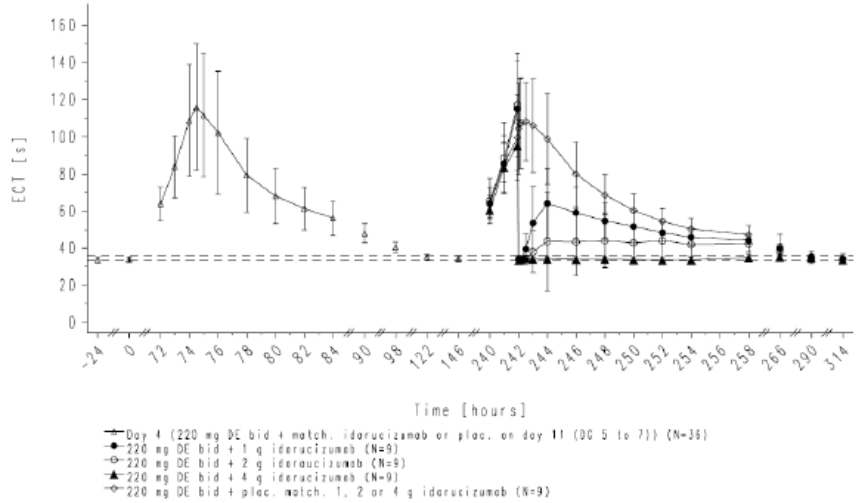
- 1 g idarucizumab resulted in immediate and complete reversal as determined by dTT, ECT, aPTT and TT. By 1 h after end of infusion, all clotting parameters showed a partial return of the dabigatran anticoagulant effect.
- 2 g idarucizumab resulted in immediate and complete reversal as determined by 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 reversal of dabigatran anticoagulation was also evidenced by a dose-dependent reduction of the ratio between the mean area under the effect curve (AUECabove,2-12) after idarucizumab infusion on Day 11 and before idarucizumab infusion on Day 4 (Table 2.1.3: 2).

Table 2.1.3: 2 Arithmetic mean $AUEC_{above,2-12}$ ratio (post-Ida/pre-Ida) for the coagulation measurements dTT, ECT, aPTT, TT, and ACT

	Ratio of Day 11/Day 4 [SD]					
	1000 to 4000 mg idarucizumab				2500+2500 mg idarucizumab	
$AUEC_{above,2-12}$ [h]	DE + Placebo	DE + 1000 mg	DE + 2000 mg	DE + 4000 mg	DE + 2 doses Pla	DE + 2500+2500 mg
dTT	1.16 [0.615]	0.29 [0.157]	0.13 [0.121]	0.02 [0.0018]	0.79 [0.430]	0.01 [0.011]
ECT	1.26 [0.679]	0.35 [0.139]	0.15 [0.130]	0.018 [0.015]	0.84 [0.386]	0.01 [0.007]
aPTT	1.26 [0.550]	0.47 [0.192]	0.18 [0.176]	0.05 [0.108]	0.88 [0.161]	0.02 [0.044]
TT	1.09 [0.388]	0.40 [0.183]	0.15 [0.225]	0.00 [0.002]	0.85 [0.322]	0.00 [0.002]
ACT	1.73 [1.897]	0.33 [0.133]	0.09 [0.143]	0.00 [0.004]	0.89 [0.340]	0.01 [0.029]

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.
Source data: [c03026940, Table 11.2.3.5: 1]



----: mean of baseline, 33.4 sec and upper limit normal reference values (mean+2*SD), 36.3 sec
Source: [c03026940, Figure 15.7.5.3.2: 4]

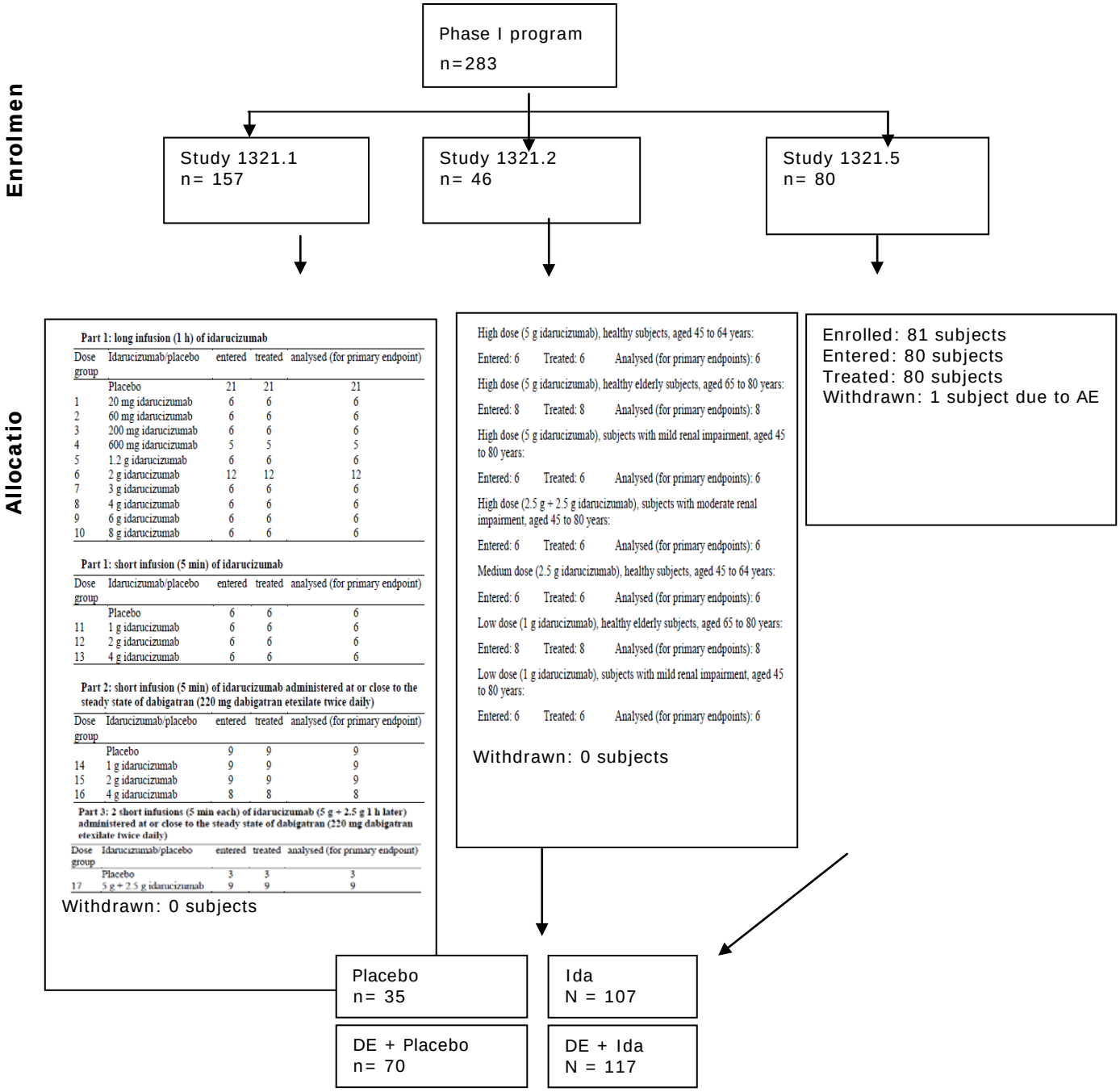
Figure 2.1.3: 2 Mean effect-time profiles (+/- SD) of ECT after multiple oral administration of 220 mg DE bid with single i.v. infusion of 1, 2, 4 g idarucizumab or placebo over 5 min at planned time 241 hours and 55 min (1 hour and 55 min after last dabigatran dose)

Administration of idarucizumab in the absence of DE did not lead to any effect on coagulation parameters and furthermore did not show any pro-thrombotic effect. The reversal effect of idarucizumab on dabigatran induced clotting was shown in this Japanese study in all dose groups. In the lower doses of 1g and 2g, a partial return of anticoagulant effect occurred. In the higher dose groups of 4g and 2.5g + 2.5g an immediate, complete and sustained reversal was observed. The data in the Japanese healthy volunteers support the efficacy of idarucizumab.

Results of phase I studies combined

In this section the effect of idarucizumab after i.v. administration in the presence of dabigatran in the Phase I studies was summarized and discussed. All doses (1 g-7.5 g) were considered. To support an integrated efficacy assessment, Phase I studies were pooled and results for subjects treated with idarucizumab and/or placebo following dabigatran etexilate pre-treatment (pretreatment not randomized) were discussed.

- **Participant flow**



The Phase I clinical development program for idarucizumab comprised 283 treated subjects in 3 studies. Approximately half of the 283 treated subjects participated in trial 1321.1 (157 subjects), about one sixth

(46 subjects) participated in the crossover trial 1321.2, and about one third of the subjects (80 subjects) were included in the Japanese and trial 1321.5. Similar proportions of subjects from each Phase I study contributed to the treatment group DE+Ida. 70 subjects were treated with DE+Placebo. 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. Subjects pretreated with DE received a maximum dose of 7.5 g idarucizumab; however, the highest dose category has an upper boundary of 8 g. The highest dose of 8 g was administered only to subjects without DE pre-treatment. Of note, in the cross-over design study 1321.2 subjects received both idarucizumab and placebo treatments, thus these individual subjects were counted twice in the combined analysis. 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. (Table 3.1.1: 1).

Table 3.1.1: 1 Summary of baseline demographics from Phase I studies combined. Subjects pretreated with DE.

	Placebo	Idarucizumab after DE			
		1 g to <2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Number of subjects N (%)	70 (100.0)	50 (100.0)	23 (100.0)	35 (100.0)	9 (100.0)
Study					
1321.1		18	8	0	9
1321.2		14	6	26	0
1321.5		18	9	9	0

Subjects from crossover study 1321.2 are counted in more than one treatment group.
Source: c03076582, Table 1.1

- **Conduct of the studies**

Treatment compliance in the Phase I studies

The study medication was always taken by the subjects under direct supervision of the investigator or one of his authorised designees. Determination of idarucizumab concentrations in plasma and urine provided additional information on treatment compliance.

Treatment compliance in Trial 1321.1

Of the 157 treated subjects, 8 subjects received the lower idarucizumab dose of the previous dose group. These 8 subjects were analysed according to the actual received dose of 2 g as 1 h infusion. Further, 2 subjects received erroneously some idarucizumab paravenously.

Treatment compliance in Trial 1321.2

Of the 46 randomised subjects in trial 1321.2, 3 subjects with mild renal impairment who were treated with 1 g idarucizumab actually received in Period 1 on Day 1 a dose of 220 mg DE instead of 150 mg DE. Of these 3 subjects, 1 subject received both in the morning and the evening a dose of 220 mg DE whereas 2 subjects received the incorrect DE dose of 220 mg only in the morning and were correctly dosed with 150 mg DE in the evening.

Treatment compliance in Trial 1321.5

Of the 80 treated subjects, all subjects were compliant with the study medication intake.

- **Baseline data**

Baseline characteristics for the combined Phase I analysis are provided in Table 3.1.3: 1.

Table 3.1.3: 1 Summary of baseline characteristics by dose category, subjects pre-treated with DE

	DE + Ida				DE + Ida	DE+placebo
	1g to <2.5g	≥2.5g - <5g	5g	>5g - 8g	all doses	
Number of subjects [N (%)]	50 (100)	23 (100	35 (100)	9 (100)	117 (100)	70 (100.0)
Sex [N (%)]						
Female	6 (12.0)	3 (13.0)	10 (28.6)	0 (0.0)	19 (16.2)	19 (27.1)
Male	44 (88.0)	20 (87.0)	25 (71.4)	9 (100.0)	98 (83.8)	51 (72.9)
Race subjects [N (%)]						
Asian	19 (38.0)	9 (39.1)	9 (25.7)	0 (0.0)	37 (31.6)	13 (18.6)
Black/African American	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (0.9)	1 (1.4)
White	31 (62.0)	14 (60.9)	25 (71.4)	9 (100.0)	79 (67.5)	56 (80.0)
Age (years), Median	30.5	27	66	26	42	55
Age Group (years) [N (%)]						
≥19 - <45	35 (70.0)	16 (69.6)	9 (25.7)	7 (77.8)	67 (57.3)	23 (32.9)
≥45 - <65	4 (8.0)	7 (30.4)	7 (20.0)	2 (22.2)	20 (17.1)	17 (24.3)
≥65 - ≤80	11 (22.0)	0 (0.0)	19 (54.3)	0 (0.0)	30 (25.6)	30 (42.9)
>80	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0	0 (0.0)
CrCL (mL/min) [a]						
Min	64.067	82.973	44.342	100.92	44.342	44.342
Median	114.47	121.27	84.011	140.96	112.17	90.118
Max	212.84	157.80	156.76	150.07	212.84	169.43
CrCL Group [N (%)] [a]						
≥30 - <50 (Moderate)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1 (0.9)	1 (1.4)
≥50 - <80 (Mild)	7 (14.0)	0 (0.0)	12 (34.3)	0 (0.0)	19 (16.2)	18 (25.7)
≥80 (Normal)	43 (86.0)	23 (100.0)	22 (62.9)	9 (100.0)	97 (82.9)	51 (72.9)
Weight (kg), Mean	70.5	72.4	71.1	74.7	71.4	73.3
BMI (kg/m^2), Mean	23.4	23.5	24.4	23.5	23.7	24.9

Source Table: c03076582, Table 1.2.1

[a] Based on Cockcroft-Gault formula

Within each Phase I trial, the demographic characteristics were balanced across the subject Groups. However, 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. In the pooled phase I data only 19 women are included in contrast to 264 male participants. 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, reflecting the similar inclusion criteria in all 3 studies.

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. Median creatinine clearance (calculated using Cockcroft-Gault formula) was lowest in subjects treated with 5 g idarucizumab (median 84.011 mL/min; min-max:

44.342-156.76). Subjects with renal impairment were only included in trial 1321.2. The categorisation for renal impairment differed between study and project levels: In trial 1321.2, the categorisation of mild renal impairment referred to a CrCl of ≥60 to <90 mL/min (12 subjects) and for moderate renal impairment (6 subjects) to a CrCl of ≥30 to <60 mL/min at the screening visit whereas the pooled analysis used a threshold of 50 mL/min to separate mild from moderate renal impairment and a threshold of 80 mL/min to separate normal renal function from mild renal impairment. As a consequence, 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. In conclusion, numbers of patients with mild or moderate renal impairment were rather small (n=20) and limited the possible conclusions to be drawn.

Dabigatran exposure at start of idarucizumab treatment

Sum dabigatran concentrations at start of idarucizumab administration are presented in Table 3.1.6: 1. Combining all groups, median sum dabigatran concentration was 235 ng/mL (min-max: 66.3-481 ng/mL. Median sum dabigatran concentrations were highest prior to administration of the 5 g dose (253.0 ng/mL).

Table 3.1.6: 1 Sum dabigatran concentration at start of idarucizumab infusion

		Idarucizumab after DE			
	Placebo	<2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Number of subjects N (%)	69	50	23	35	8
gMean (ng/mL)	218.1	213.2	203.8	260.2	155.6
gCV (%)	40.9	51.4	33.9	35.5	37.8
Min (ng/mL)	77.7	66.3	88.3	101.0	89.1
25th percentile (ng/mL)	168.0	153.0	180.0	211.0	121.0
Median (ng/mL)	222.0	239.0	216.0	253.0	146.5
75th percentile (ng/mL)	300.0	304.0	242.0	341.0	219.0
Max (ng/mL)	516.0	481.0	318.0	479.0	257.0

Source Table: [c03076582, Table 1.4.1]

The median sum dabigatran concentrations at start of idarucizumab treatment present a very large baseline range min-max: 66.3-481ng/ml. Median levels were however comparable in all idarucizumab dose groups. The applicant is asked to present in which way the differences in dabigatran baseline levels might have influence on the efficacy of the proposed idarucizumab dose.

- **Numbers analysed**

The vast majority of subjects received idarucizumab as single dose infusion (79.5%,), 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. Given that in the pooled phase I studies, only 9 subjects (7.7%) were treated with 2 single infusions of 2.5g+2.5g idarucizumab given 15 min apart. Therefore, the experience with the proposed dosing regimen in healthy volunteers is very limited.

- **Outcomes and estimation**

Coagulation times at baseline and at start of idarucizumab infusion

Mean baseline coagulation times in the absence of dabigatran as well as at steady state just before administration of idarucizumab are provided in Table 3.2.1: 1. Across dose groups, mean baseline coagulation times as well as dabigatran-induced anticoagulation were similar for the individual assays. However, coagulation times of all assays appeared slightly lower prior to administration of the highest idarucizumab dose (>5 g to ≤8 g).

Table 3.2.1: 1 Coagulation times at baseline and at start of idarucizumab infusion (pre-dose) for all coagulation assays. Mean (SD) values are presented.

		Idarucizumab after DE			
	Placebo	<2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Number of subjects N (%)	70	50	23	35	9
Primary parameters					
dTT - baseline [s]	32.0 (2.0)	31.4 (1.5)	32.2 (2.5)	31.5 (1.4)	33.2 (2.6)
dTT - pre-dose ida [s]	61.9 (11.9)	61.8 (12.6)	59.5 (7.9)	65.2 (10.2)	48.7 (7.3)
ECT – baseline [s]	35.0 (2.1)	35.5 (3.0)	35.0 (1.9)	34.9 (2.2)	36.8 (1.4)
ECT – pre-dose ida [s]	105.6 (27.0)	105.0 (29.6)	97.4 (16.6)	116.7 (31.5)	92.7 (19.6)
Further parameters					
TT – baseline [s]	12.5 (0.7)	12.5 (0.8)	12.7 (0.7)	12.4 (0.5)	12.9 (0.9)
TT – pre-dose ida [s]	130.7 (36.1)	132.7 (50.1)	129.0 (32.6)	138.5 (47.4)	111.5 (19.3)
aPTT – baseline [s]	31.6 (4.2)	32.5 (4.4)	32.7 (3.5)	32.0 (4.0)	35.1 (1.7)
aPTT – pre-dose ida [s]	67.6 (13.1)	71.0 (15.9)	66.5 (12.3)	69.3 (10.8)	65.0 (9.2)

Source Tables: c03076582, Table 3.1.1; Table 3.2.1; Table 3.3.1; Table 3.4.1
ida, idarucizumab

All parameters regarding coagulation time at baseline after DE administration are in the same range with similar mean standard deviations in the different dose levels. This is also true for coagulation parameters at start of idarucizumab infusion. This allows a comparison of the idarucizumab effect in the different dose levels.

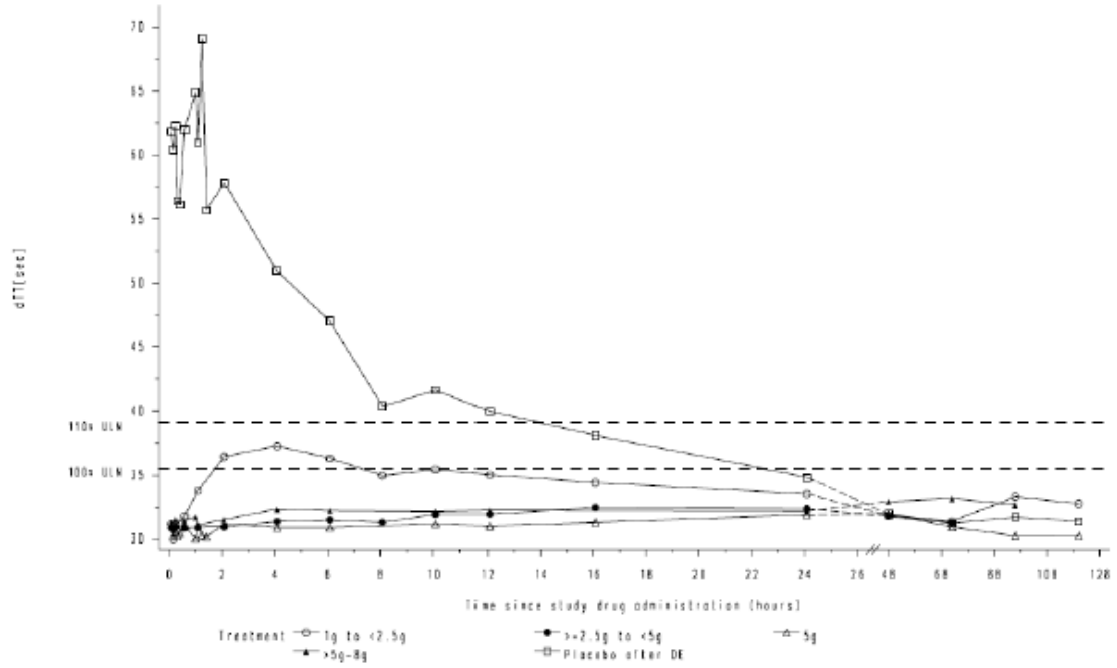
Proportion of subjects achieving complete reversal

Data on the proportion of subjects with complete reversal based on 100% ULN within 4 hours since start of idarucizumab infusion is presented in Table 3.2.2: 1. Consistently over analyses across all dose groups and using both thresholds, 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 (for a graphical presentation refer to Figures 3.2.2: 1 and 3.2.2: 2). Similar results were obtained for the further parameters TT and aPTT. Of note, 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.

Table 3.2.2: 1 Proportion of subjects achieving complete reversal based on 100% ULN within 4 hours since start of idarucizumab infusion.

	Placebo	Idarucizumab after DE			
		1 g to <2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Number of subjects N (%)	69 (100.0)	50 (100.0)	23 (100.0)	35 (100.0)	8 (100.0)
Primary parameters					
dTT	1.4	100.0	100.0	100.0	100.0
95% CI [%]	(0.3, 7.8)	(92.9, 100.0)	(85.7, 100.0)	(90.1, 100.0)	(67.6, 100.0)
ECT	0	100.0	100.0	97.1	100.0
95% CI [%]	(0, 5.3)	(92.9, 100.0)	(85.7, 100.0)	(85.5, 99.5)	(67.6, 100.0)
Further parameters					
TT	0	96.0	100.0	97.1	100.0
95% CI [%]	(0, 5.3)	(86.5, 98.9)	(85.7, 100.0)	(85.5, 99.5)	(67.6, 100.0)
aPTT	2.9	96.0	91.3	94.3	100.0
95% CI [%]	(0.8, 10.0)	(86.5, 98.9)	(73.2, 97.6)	(81.4, 98.4)	(67.6, 100.0)

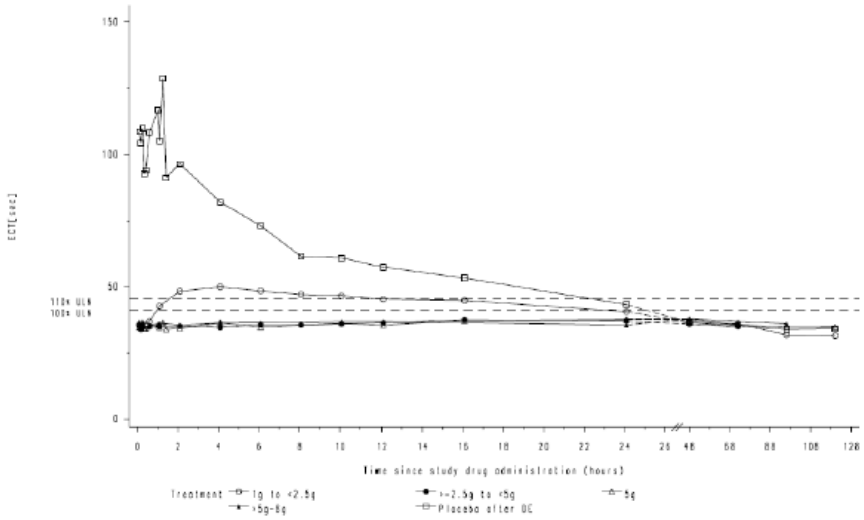
Reversal is calculated as 100 * (pre−dose value minus post−dose value)/(pre−dose value minus ULN); if calculated reversal was > 100, it was set to 100; if calculated reversal was < 0, it was set to 0. For study 1321.2, PD data obtained after start of the re−administration of DE were excluded. The 95% confidence intervals are computed using the Wilson score method. Subjects from crossover study 1321.2 are counted in more than one treatment group.
Source Tables: [c03076582, Table 2.1.10] [Table 2.2.10] [Table 2.3.10] [Table 2.4.10]



Source: [c03076582, Figure 3.1.4]

For study 1321.2, data obtained after start of DE re-administration were excluded; time point 0 refers to end of idarucizumab infusion

Figure 3.2.2: 1 Mean dTT-time profiles by planned time from Phase I studies combined. Subjects pre-treated with DE and had PD measurements.



Source: c03076582, Figure 3.2.4

For study 1321.2, data obtained after start of DE re-administration were excluded; time point 0 refers to end of idarucizumab infusion

Figure 3.2.2: 2 Mean ECT-time profiles by planned time from Phase I studies combined. Subjects pre-treated with DE and had PD measurements.

The complete reversal of the effect of DE treatment measured with the coagulation assays dTT, ECT, TT and aPTT is shown for nearly all of the participating subjects. This data show that idarucizumab is able to reverse the effect of dabigatran etexilate. However, the applicant was asked if there are any possibly known reasons why some subjects did not gain a complete reversal. The applicant presented a conclusive reworking of the patient cases with incomplete reversal. The conclusions drawn were that incomplete reversal resulted from an individual patient's baseline above the pre-specified ULN for a specific assay. In exceptional cases incomplete reversal may result from a dabigatran body load that exceeds the binding capacity of 5 g idarucizumab. The rare case that dabigatran body load might exceed the binding capacity of idarucizumab could be managed with a second dose in case of clinical need.

Time to complete reversal

Time to complete reversal was summarized for subjects who have achieved complete reversal within 4 hours since start of idarucizumab infusion. The results are summarized in Table 3.2.3: 1 (100% 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 3.2.3: 1 Summary of time [minutes] to achieve complete reversal for subjects achieving complete reversal based on 100% ULN

Time [minutes] to achieve complete reversal		Placebo	Idarucizumab after DE			
			1 g to <2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Primary parameters						
dTT	N	1	50	23	35	8
	Median	15.0	5.0	5.0	6.0	5.0
ECT	N	0	50	23	34	8
	Median	-	5.0	5.0	6.0	5.0
Further parameters						
TT	N	0	48	23	34	8
	Median	-	5.0	5.0	6.0	5.0
aPTT	N	2	48	21	33	8
	Median	35.0	5.0	5.0	6.0	5.0

Reversal is calculated as 100 * (pre−dose value minus post−dose value)/(pre−dose value minus ULN); if calculated reversal was > 100, it was set to 100; if calculated reversal was < 0, it was set to 0. For study 1321.2, PD data obtained after start of the re−administration of DE were excluded. Subjects from crossover study 1321.2 are counted in more than one treatment group. Time to reversal was computed using the actual time (not planned time).
Source Tables: c03076582, Table 2.1.14; Table 2.2.14; Table 2.3.14; Table 2.4.14

The reversal effect of idarucizumab was seen very soon with a median onset 5 minutes after the start of the infusion. This was considered very important for the clinical effect of the product.

Duration of reversal

For subjects who achieved complete reversal, summary statistics of duration of complete reversal are presented in Table 3.2.4: 1 (100% ULN). 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. Duration of complete reversal based on TT was shorter compared to the other coagulation assays in all dose groups. This is considered to result from the used very narrow ULN.

Table 3.2.4: 1 Summary of duration [hours] of complete reversal based on 100% ULN for subjects achieving complete reversal.

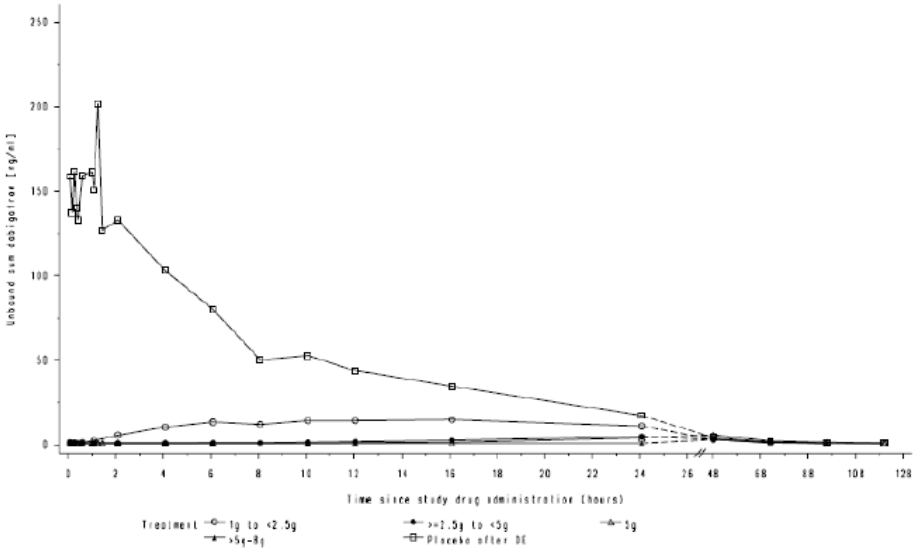
Duration [hours] of complete reversal		Placebo	Idarucizumab after DE			
			1 g to <2.5 g	2.5 g to <5 g	5 g	>5 g to ≤8 g
Primary parameters						
dTT	N	1	50	23	35	8
	Mean (SD)	0.7 (-)	34.5 (35.0)	55.8 (25.3)	58.6 (23.4)	69.0 (8.5)
	Median	0.7	4.0	72.0	72.0	72.0
ECT	N	0	50	23	34	8
	Mean (SD)	-	18.2 (28.0)	47.3 (29.3)	51.6 (27.3)	69.0 (8.5)
	Median	-	4.0	72.0	72.0	72.0
Further parameters						
TT	N	0	48	23	34	8
	Mean (SD)	-	9.9 (20.2)	29.0 (24.8)	29.5 (17.9)	63.0 (12.4)
	Median	-	2.0	16.0	24.0	72.0
aPTT	N	2	48	21	33	8
	Mean (SD)	0.6 (0.6)	25.3 (32.2)	54.2 (26.3)	51.0 (29.0)	63.1 (25.1)
	Median	0.6	4.0	72.0	72.0	72.0

Reversal is calculated as 100 * (pre−dose value minus post−dose value)/(pre−dose value minus ULN); if calculated reversal was > 100, it was set to 100; if calculated reversal was < 0, it was set to 0. For study 1321.2, PD data obtained after start of the re−administration of DE were excluded. Subjects from crossover study 1321.2 are counted in more than one treatment group. Duration was computed using the actual time (not planned time) and was truncated at 72 hours.
Source Tables: c03076582, Table 2.1.11; 2.2.11; 2.3.11; 2.4.11

Mean duration on complete reversal for doses >2.5g was >50 hours and the median duration of complete reversal for dTT and ECT was 72h. This duration of complete reversal is long enough to fulfil the requirements of a reversal agent in an emergency situation like bleedings or emergency operations.

Unbound sum dabigatran

Although unbound sum dabigatran concentrations represent a pharmacokinetic rather than a pharmacodynamic measurement, these are considered supportive information. Before idarucizumab infusion, dabigatran concentrations were similar across groups (Table 3.1.6: 1). The effect of idarucizumab on gMean unbound sum dabigatran is depicted in Figure 3.2.5: 1. 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. In the dose group 1 to <2.5 g idarucizumab, a small reoccurrence of unbound sum dabigatran concentrations was observed. This was expected as the doses in that combined group were around or below the calculated dose equimolar to total dabigatran body load. Geometric mean unbound sum dabigatran concentrations in that group did not exceed 15 ng/mL.



Source: [c03076582, Figure 4.4]

For study 1321.2, data obtained after start of DE re-administration were excluded; time point 0 refers to end of idarucizumab infusion

Figure 3.2.5: 1 Geometric mean unbound sum dabigatran concentration time profiles by planned time from Phase I studies combined. Subjects pre-treated with DE and had PD measurements.

After administration of idarucizumab in doses >2.5g, the sum of unbound dabigatran was at the LLOQ/ near 1ng/ml. These findings support the efficacy of idarucizumab.

- **Ancillary analyses**

Comparison of phase I results in subpopulations

Effect of sex

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.

Effect of age

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.

Effect of renal impairment

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. Administration of a total dose of 5 g idarucizumab resulted in sustained reversal of coagulation times.

Effect of race

Administration of a total dose of 5 g idarucizumab resulted in sustained reversal of coagulation times in both Japanese and Caucasian subjects.

For all the presented subpopulations regarding sex, age, underlying diseases and race, the numbers of assessed subjects was considered too small to draw a final conclusion.

Anti-drug antibodies

The presence of anti-idarucizumab antibodies before and after treatment was evaluated in all Phase I studies at baseline, end-of-study visit (2-11 days), 4 weeks, and 3 months post-treatment. In study 1321.2, 6 subjects underwent re-exposure to idarucizumab 2 months after a first exposure, so an additional sampling point was added. 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 titers, 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.

18 of 224 subjects (8.0%) treated with idarucizumab in the Phase I studies had treatment emergent anti-idarucizumab antibody responses. Responses were characterized as weak (i.e. low titer, maximum titer=40) and mostly non-blocking, with an even distribution between transient and possibly persistent responses. Based on these observations, it was concluded that idarucizumab has a low immunogenic potential.

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, the amount of anti-idarucizumab antibody in circulation could be estimated and compared to the dose of idarucizumab that would be administered. For a titer of 40 (corresponding to roughly 3.3 µg/ml 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 was considered that the dose is overwhelming in comparison to the estimated maximum concentration of treatment-emergent anti-idarucizumab antibodies observed to date. Therefore, it was 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.

The CHMP agreed that the applicant presented a “worst case scenario” showing that even subject with a titer of 40 will receive with a 5g dose of idarucizumab enough drug to overwhelm a possible ADA effect on efficacy. This was comprehensible and therefore the amount of ADA measured, was not regarded as a concern in the current setting.

Study 1321.3; REVERSE AD [ongoing]) – results of the interim analysis with the cut-off for recruitment: 1 April, 2015

A Phase III, case series clinical 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)

Methods

1321.3 is an open label, uncontrolled, case series, multi-centre study. It is planned to treat approximately 200 to 300 patients with a total dose of 5 g (two 2.5g vials) of idarucizumab. Patients receive a 2.5 g vial of study medication and a second 2.5 g vial within the next 15 minutes. 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.

The study is still ongoing. Overall cut-off date for the first interim report (N=26): 2 Dec 2014, cut-off for central lab PK/PD data (N=13): 12 Sep 2014. The second interim analysis of RE-VERSE AD was included in the responses to the Day 120 LoQ. It included clinical data from 123 patients recruited into RE-VERSE AD up to April 01, 2015 and central laboratory data for assessment of efficacy that were available for 90 patients.

Efficacy assessment in this study was 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 hemostasis during surgery, thrombotic events and deaths were also recorded.

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.

Study participants

Inclusion criteria

Patients taking DE were eligible for this study if they were ≥18 years at entry, signed the informed consent, and either had an overt bleeding which was judged by the physician to require a reversal agent (Group A) or were in a condition requiring emergency surgery or invasive procedure where adequate haemostasis was required (Group B). Emergency was defined as within the following 8 h.

Exclusion criteria

Patients were excluded if they fulfilled the following criteria:

Group A

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

- Patients with no clinical signs of bleeding
- Contraindications to study medication including known hypersensitivity to the drug or its excipients (patients with hereditary fructose intolerance may react 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 including known hypersensitivity to the drug or its excipients (patients with hereditary fructose intolerance may react to sorbitol)

The CHMP agreed that the inclusion and exclusion criteria are adequate to define the planned target population. The amount of sorbitol was very high with 2g in one 50mL vial. So each patient should receive 4g of sorbitol with the planned target dose. This was considered as a very high risk and was reflected in the SmPC.

Treatments

Patients receive a 2.5 g vial of study medication and a second 2.5 g vial within the next 15 minutes. 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.

Objectives

The primary objective was to demonstrate reversal of the anticoagulant effect of dabigatran. The secondary objectives were the assessment of bleeding, clinical outcomes, safety and the pharmacokinetics of dabigatran in the presence of idarucizumab.

Outcomes/endpoints

The efficacy evaluation of the interim data of study 1321.3 focused on the primary endpoint of maximum reversal of centrally assessed dTT and ECT, supported by aPTT and TT. The primary study endpoint was the maximum reversal 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.

In addition, the following summaries were provided:

- 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
- The proportion of patients that achieved at least 100%, 80%, and 50% reversal (dTT, ECT, TT, aPTT)
- Unbound sum dabigatran concentration by time for patients with available PK measurements

The reversal effect of idarucizumab using dTT, ECT, TT and aPTT from central lab was evaluated similarly as for the Phase I studies, however only for patients whose baseline PD values were above 110% ULN or ULN. These patients were referred to as "evaluable patients". Values of PD markers with ≥100% reversal were interpreted as complete reversal of the anticoagulant effect.

Clinical outcomes, as assessed by the treating clinicians, were secondary end points. The clinical assessment for bleeds (cessation of bleeding for patients in Group A and occurrence of major bleeding in patients in Group B) and other outcome events such as death were obtained from patients' narratives, AEs and SAEs listing and were presented as a brief summary per individual patient. For the interim analyses, no central adjudication of clinical outcomes was performed.

Sample size

This was a second pre-planned interim analysis from an ongoing single arm study planned to include 200 – 300 patients. The analysis of the second interim analysis submitted with the responses to the D120 LoQs was based on clinical data from 123 patients (central laboratory data for 90 patients).

Statistical Analysis

The maximum percentage reversal was calculated for patients with pretreatment dTTs or ECTs above the upper limit of the normal range, with the use of descriptive statistics with confidence intervals or percentiles as appropriate. Clotting-time measurements that exceeded the maximum measurable range were imputed with the use of the maximum measurable clotting time of 500 seconds only if the imputation was consistent with the concomitant results of other coagulation tests and unbound-dabigatran concentrations. Analyses were stratified by group and (where appropriate) by time.

Results

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 intravenous 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 (Table 15.1.4: 1). 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 hours.

Demographic and baseline data

Table 1.3: 1 Demographics of Patients in 1321.3

Characteristic	Group A	Group B	Total
Number of subjects	66	57	123
Male N (%)	37 (56.1)	28 (49.1)	65 (52.8)
Race N (%)			
Asian	6 (9.1)	2 (3.5)	8 (6.5)
Black/African American	1 (1.5)	0 (0)	1 (0.8)
Hawaiian/Pacific Islander	3 (4.5)	4 (7.0)	7 (5.7)
White	54 (81.8)	51 (89.5)	105 (85.4)
Missing	2 (3.0)	0 (0)	2 (1.6)
Age (years)			
Median	77	77	77
(min, max)	(48, 93)	(50, 93)	(48, 93)
Weight (kg) N	62	54	116
Median	70.5	75.5	71.8
(min, max)	(42.4, 128)	(40, 150)	(40, 150)
Creatinine Clearance by Cockroft-Gault (mL/min)	58	53	111
Mean (SD)	59.3 (33.4)	63.7 (39.5)	61.4 (36.3)
Median (min, max)	52.7 (12.1, 187)	57.3 (11.4, 193)	55.1 (11.4, 193)
N (%)			
< 30	7 (10.6)	12 (21.1)	19 (15.4)
>= 30 - < 50	20 (30.3)	10 (17.5)	30 (24.4)
>= 50 - < 80	20 (30.3)	18 (31.6)	38 (30.9)
>= 80	11 (16.7)	13 (22.8)	24 (19.5)
Missing	8 (12.1)	4 (7.0)	12 (9.8)
Daily dose of dabigatran (N%)			
110 mg BID	44 (67.7)	36 (63.2)	80 (65.0)
150 mg BID	19 (28.8)	18 (31.6)	37 (30.1)
75 mg BID	1 (1.5)	0 (0)	1 (0.8)
Other	2 (3.0)	3 (5.3)	5 (4.1)
Dabigatran indication (N%)			
Atrial fibrillation	62 (93.9)	55 (96.5)	117 (95.1)
Orthopedic surgery	0 (0)	0 (0)	0 (0)
Venous thromboembolism	1 (1.5)	1 (1.8)	2 (1.5)
Other	3 (4.5)	1 (1.8	4 (3.3)
Time since last dabigatran intake			
Median (hours)	13.8	17.6	15.6
N(%)			
<12	22 (33.3)	18 (31.6)	40 (32.5)
12 - <24	28 (42.4)	18 (31.6)	46 (37.4)
24-<48	15 (22.7)	17 (29.8)	32 (26.0)
>48	1 (1.5)	4 (7.0)	5 (4.1)
Type of bleeding (group A) N(%)			
Intracranial	24 (36.4)	-	24
Trauma-related	12 (18.2)	-	12
Gastrointestinal	27 (40.9)	-	27

Source data Table 15.1.3.1: 1 and 15.1.3.1: 2.

Table 1.3: 2 Evaluable patients for central laboratory assessment of efficacy.

Central Laboratory Test*	Group A (N=51)	Group B (N=39)	Total (N=90)
Elevated dTT at baseline N (%)	40 (78.4)	28 (71.8)	68 (75.6)
Elevated ECT at baseline N (%)	47 (92.2)	34 (87.2)	81 (90)
Elevated TT at baseline N (%)	49 (96.1)	37 (94.9)	86 (95.6)
Elevated aPTT at baseline N (%)	39 (76.5)	26 (66.7)	65 (72.2)

*only available for the 90 patients with central laboratory data
Source: Tables 15.2.1.1.1: 2, 15.2.1.2.1: 2, 15.2.2.4.1: 2, and 15.2.2.4.2: 2

In this study, the bleeding patients (Group A) had slightly worse renal function (median CrCl= 52.7 mL/min) compared to the surgical patients (Group B, 57.3 mL/min). The primary indication for treatment with DE was stroke prevention in patients with AF. Ninety-five percent of patients entered to date were being treated for this indication. The most common dose of DE was 110 mg bid (65% of patients).

The median time between the last dose of DE 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 hours. This estimate of time since the last dose of DE was 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 also 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 AF 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. Against a background diagnosis of AF, a median age of 77 years and poor renal function in many patients, this was clearly a population with a high underlying risk for stroke, bleeding, and death.

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. This finding confirms that all patients had taken DE.

The details of the bleeding events leading to treatment Group A (bleeding)

Table 1.3.1: 1 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)

Source: Table 15.1.3.1: 3

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. Bleeding may have occurred in more than one location. The 24 ICHs were classified as intracerebral (N=14), subdural (N=9) or subarachnoid (N=6). In several cases the ICH occurred in more than one location. The median

Glasgow Coma Scale was 14.0 (range 3 to 15). For the 27 gastrointestinal bleeds, 10 were identified as upper GI, 8 as lower GI, and 9 could not be localized.

The indications for surgery Group B (surgery)

There were 57 patients allocated to the surgery/invasive procedure group (Group B). The indications for surgery are listed in Table 1.3.2: 1. There were 3 patients who did not undergo the planned surgery. Idarucizumab obviated the need for emergency dialysis in 1 patient in group B who had ingested a massive overdose of dabigatran; the condition of 2 other patients in group B remained too unstable for surgery despite the reversal of anticoagulation. For 52 evaluable patients, the median time between administration of the first vial and the start of surgery was 1.7 hours (range: -0.2 hours to 26.4 hours).

Table 1.3.2: 1 Indications for surgery/interventional procedure

Indication for Surgery	Frequency
Bone fractures	13
Acute cholecystitis, cholelithiasis, icterus	7
Acute renal insufficiency, catheter placement for dialysis	5
Joint/wound infection	4
Acute appendicitis	3
Small bowel obstruction	3
Probable perforation of the viscera	3
Abscess (suprapubic, scrotal)	2
Acute mesenteric ischemia	2
Cardiac arrhythmias	2
Aortic dissection	1
Aortic aneurysm	1
Acute deterioration of aortic valve	1
Gastrointestinal bleed	1
Incarcerated umbilical hernia	1
Lumbar puncture	1
Left leg gangrene	1
Pericardial tamponade	1
Pneumothorax	1
Peritonitis	1
Unstable angina	1
Ureteric obstruction, hydronephrosis	1
Missing	1
Total	**57**

Source: Appendix 16.2.1 Listing 3

Normalization of clotting tests

At entry, the dTT was normal in 22 patients, of whom 9 also had normal ECTs. 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 dTT and ECT. This narrow confidence interval was due to the fact that most of the patients (>89%) achieved complete reversal. The reversal was evident immediately after administration of the first vial.

Normalization of clotting tests was defined as those tests with values equal to or below the upper limit of normal. The dTT was normalized in 97.5% and 92.9% of evaluable patients in Groups A and B, respectively, whereas the ECT was normalized 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 contributed to the observed differences.

At 12 and 24 hours, dTT were below the upper limit of normal in 90.2% and 80.7% of available patients, respectively, while the ECT 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 activated partial thromboplastin time (aPTT) measured in the central laboratory or at the local hospitals based on local ULN. For both the central laboratory and local laboratory determination of aPTT, median maximum reversal was 100% (95% CI, 100-100). Using central assessment of aPTT, normalization was achieved in 94.9% and 84.6% of patients in Groups A and B within 4 hours, respectively, compared to 75.0% and 75.6% when determined by the local laboratory within 30 minutes. Local aPTT was measured only at baseline, after the first vial, 10-30 minutes after the second vial, and after 12 hours. Agreement between local and central lab results would only be expected if the samples were collected at the same time points and analysed with the same methods.

Clinical outcomes

Hospitalization

For the 123 treated patients, data on hospitalization were available for 112. ICU stay was recorded for 116. The median duration in the ICU was 0 days (range: 0 to 44). There did not appear to be relevant differences between Groups A and B.

Bleeding Status

In Group A, bleeding cessation was determined by the investigator/treating physician in 48 of 66 patients (73%). For 18 patients (27%), no assessment of the bleed cessation could be made at any time during the study due to inability to visualize or identify the bleeding site. Cessation was subjective and based upon whatever the investigator could visualize 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). 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 hemostasis. For 3 patients (5.8%), mildly abnormal intraprocedural hemostasis (e.g. slight oozing) occurred and 1 patient (1.9%) was judged to have moderately abnormal hemostasis (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.

Re-starting 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 type and frequency of antithrombotic treatment is shown in Table 2.3: 2.

Table 2.3: 2 Re-starting antithrombotic therapy after idarucizumab treatment, Study 1321.3 (number of patients)

Antithrombotic	Group A (N=66) Frequency	Group B (N=57) Frequency
Any antithrombotic	47	49
Dabigatran etexilate*	17	34
Low-molecular-weight heparin	24	39
Unfractionated heparin	13	9
Aspirin	10	8
Clopidogrel	0	2
Apixaban	3	2
Rivaroxaban	2	0
Warfarin	4	1
None	15	1
Missing	4	7

Patients may be counted in more than one category
*patients may be bridged with heparin or low molecular weight heparin prior to dabigatran
Source: Table 15.1.3.1: 7 and 15.2.3.4: 2

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of efficacy for trial 1321.1

Title: Study 1321.1		
Study identifier	1321.1	
Design	Randomised, double-blind, placebo-controlled within dose groups, Phase 1	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	72 hours not applicable not applicable
Hypothesis	Exploratory: safety, tolerability and PK of single rising IV doses of idarucizumab (20 mg to 8 g) was investigated	
Treatments groups	Part 1	Healthy male volunteers: IV idarucizumab: 20 mg to 8 g (1 h inf., 10 steps), 1, 2, 4 g (5 min inf.), no prior DE treatment, N=110, Ida:placebo 6:2
	Part 2	Healthy male volunteers: IV idarucizumab: 1, 2, 4 g (5 min inf.), prior DE 220 mg bid, N=35, Ida:placebo 9:3
	Part 3	Healthy male volunteers: IV idarucizumab: 5 g + 2.5 g (60 min later, 5 min inf.), prior DE 220 mg bid, N=12, Ida:placebo 9:3

Endpoints and definitions	dTT ECT	PD biomarkers	Diluted Thrombin Time Ecarin Clotting Time		
	aPTT TT	PD biomarkers	Activated Partial Thromboplastin Time Thrombin Time		
Database lock	30 Jan 2014				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Descriptive statistics, N=157				
Descriptive statistics and estimate variability	Treatment group	Part 1	Part 2	Part 3	
	Number of subject	110	35	12	
	Unbound sum dabigatran concentrations	NA	Dropped to or below LLOQ	Dropped to or below LLOQ	
	dTT	Unchanged	Reversal to ULN	Reversal to ULN	
	ECT	Unchanged	Reversal to ULN	Reversal to ULN	
	aPTT	Unchanged	Reversal to ULN	Reversal to ULN	
	TT	Unchanged	Reversal to ULN	Reversal to ULN	
Notes	Only descriptive statistics were performed				
Analysis description	**NA**				

Table 2. Summary of efficacy for trial 1321.2

Title: 1321.2		
Study identifier	1321.2	
Design	Randomised, dougle-blind, placebo-controlled, 2-way crossover, single dose, Phase 1b	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	1 week not applicable not applicable

Hypothesis	Exploratory: Safety, tolerability PK and PD of idarucizumab and to establish the efficacy of idarucizumab in reversal of dabigatran anticoagulant activity in volunteers (male:female ~ 1:1)		
Treatments groups	Healthy, 45-64 years		IV idarucizumab 2.5 g, prior DE 220 mg bid, re-dosing DE and idarucizumab, N=6
	Healthy, 45-64 years		IV idarucizumab 5 g, prior DE 220 mg bid, re-dosing DE, N=6
	Healthy elderly, 65-80 years		IV idarucizumab 1 g, prior DE 220 mg bid, N=8
	Healthy elderly, 65-80 years		IV idarucizumab 5 g, prior DE 220 mg bid, N=8
	Mild renally impaired, 45-80 years		IV idarucizumab 1 g, prior DE 150 mg bid, N=6
	Mild renally impaired, 45-80 years		IV idarucizumab 5 g, prior DE 150 mg bid, N=6
	Moderate renally impaired, 45-80 years		IV idarucizumab 2.5 + 2.5 g (one hour apart), prior DE 150 mg bid, N=6
Endpoints and definitions	dTT ECT	PD biomarkers	Diluted Thrombin Time Ecarin Clotting Time
	aPTT TT	PD biomarkers	Activated Partial Thromboplastin Time Thrombin Time
Database lock	04 Sep 2014		

Results and Analysis

Analysis description	**Primary Analysis**							
Analysis population and time point description	Descriptive statistics, N=46							
Descriptive statistics and estimate variability	Treatment group	Healthy, 45-64 years	Healthy, 45-64 years	Healthy elderly, 65-80 years	Healthy elderly, 65-80 years	Mild renally impaired, 45-80 years	Mild renally impaired, 45-80 years	Moderate renally impaired, 45-80 years
	Number of subject	6	6	8	8	6	6	6
	Unbound sum dabigatran concentrations	Dropped to or below LLOQ	Dropped to or below LLOQ	Dropped to or below LLOQ	Dropped to or below LLOQ	Dropped to or below LLOQ	Dropped to or below LLOQ	Dropped to or below LLOQ
	dTT	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN
	ECT	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN

	aPTT	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN
	TT	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN	Reversal to ULN
Notes	Only descriptive statistics were performed							
Analysis description	**NA**							

Table 3. Summary of efficacy for trial 1321.5

Title: 1321.5			
Study identifier	1321.5		
Design	Randomised, double-blind within dose groups, placebo-controlled, sequential rising order, Phase 1		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 hours not applicable not applicable
Hypothesis	Exploratory: safety and tolerability of different IV doses of idarucizumab administered alone and at the steady state of dabigatran, investigation of PK of idarucizumab		
Treatments groups	Part 1		Healthy male Japanese volunteers, IV idarucizumab, SRD with 5 min infusion of 1, 2 and 4 g and 1 h infusion of 8 g, N=32
	Part 2		Healthy male Japanese volunteers, IV idarucizumab, 5 min infusion of 1, 2 and 4 g, as well as 2 infusions of 2.5 g idarucizumab, each, 15 min apart, prior steady state of 220 mg bid DE dosing regimen, N=48
Endpoints and definitions	dTT ECT	PD biomarkers	Diluted Thrombin Time Ecarin Clotting Time
	aPTT TT	PD biomarkers	Activated Partial Thromboplastin Time Thrombin Time
Database lock	26 Sep 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Descriptive statistics, N=80		
Descriptive statistics and estimate variability	Treatment group	Part 1	Part 2
	Number of subject	32	48

	Unbound sum dabigatran concentrations	Dropped to or below LLOQ	Dropped to or below LLOQ
	dTT	Reversal to ULN	Reversal to ULN
	ECT	Reversal to ULN	Reversal to ULN
	aPTT	Reversal to ULN	Reversal to ULN
	TT	Reversal to ULN	Reversal to ULN
Notes	Only descriptive statistics were performed		
Analysis description	**NA**		

Table 4. Summary of efficacy for trial 1321.3

Title: RE-VERSE AD (RE-VERSal Effects of Idarucizumab on Active Dabigatran)			
Study identifier	1321.3		
Design	Open label, uncontrolled, case series, Phase 3 (ongoing)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		3 months not applicable not applicable
Hypothesis	Exploratory: demonstration of reversal of the anticoagulant effect of dabigatran. Assessment of bleeding, clinical outcomes, safety and the PK of dabigatran in the presence of idarucizumab		
Treatments groups	Group A		Patients treated with DE who have uncontrolled bleeding, IV idarucizumab, 2.5 + 2.5 g (15 min apart), N=11
	Group B		Patients treated with DE who have immediate need for emergency surgery or medical procedures, IV idarucizumab, 2.5 + 2.5 g (15 min apart), N=15
Endpoints and definitions	dTT ECT	PD biomarkers	Diluted Thrombin Time Ecarin Clotting Time
	aPTT TT ETP ACT	PD biomarkers	Activated Partial Thromboplastin Time Thrombin Time Endogenous Thrombin Potential Activated Clotting Time
	Clinical outcomes	Clinical observation	Cessation of bleeding (Group A) Major bleeding (Group B)

Database lock (second interim analysis)	04 Dec 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Descriptive statistics, N=26		
Descriptive statistics and estimate variability	Treatment group	Group A	Group B
	Number of subject	11	15
	dTT (N=6)	Reversal to ULN	Reversal to ULN
	ECT (N=10)	Reversal to ULN	Reversal to ULN
	aPTT (N=7)	Reversal to ULN	Reversal to ULN
	TT (N=10)	Reversal to ULN	Reversal to ULN
	ETP		
	ACT		
	Unbound sum dabidatran	Dropped to or below 1.2 ng/mL (LLOQ 1 ng/mL)	Dropped to or below 1.2 ng/mL (LLOQ 1 ng/mL)
	Cessation of bleeding	ICH (N=5, difficult to evaluate) GI bleeds (improvement (N=3), no improvement (N=1), delayed improvement (N=1), unassessable (N=1)	NA
	Major Bleeding	NA	Normal haemostasis (N=11) Mildly abnormal haemostasis (N=1) Moderately abnormal haemostasis (N=1) Intervention cancelled (N=1) Unassesable (N=1)
Notes	Only descriptive statistics were performed		
Analysis description	**NA**		

Analysis performed across trials (pooled analyses and meta-analysis)

Proportion of subjects achieving complete reversal

Data on the proportion of subjects with complete reversal based on 100% ULN within 4 hours since showed that consistently over analyses across all dose groups and using both thresholds, 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. Similar results were obtained for the further parameters TT and aPTT.

Time to complete reversal

Time to complete reversal was summarized for subjects who have achieved complete reversal within 4 hours since start of idarucizumab infusion. The results are that 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.

Duration of reversal

For subjects who achieved complete reversal it was observed that consistently over the primary parameters dTT and ECT, and supported by aPTT, the 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 as judged by the primary parameters dTT and ECT. 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.

Unbound sum dabigatran

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. In the dose group 1 to <2.5 g idarucizumab, a small reoccurrence of unbound sum dabigatran concentrations was observed. This was expected as the doses in that combined group were around or below the calculated dose equimolar to total dabigatran body load. Geometric mean unbound sum dabigatran concentrations in that group did not exceed 15 ng/mL.

Clinical studies in special populations

No special studies in e.g. children, elderly or in patients with renal or hepatic impairment were performed.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The design of the studies in healthy subjects and patients was adequate to allow an appropriate assessment of the PK and PD properties of idarucizumab alone as well as idarucizumab after DE treatment in comparison to placebo. The inclusion and exclusion criteria were adequately chosen to select the proposed population of healthy volunteers as well as elderly participants and participants with mild to moderate renal impairment. They reflect to some extent the proposed patient population, although the patients being candidates for idarucizumab treatment are likely to be older and have more co-morbidities.

The case series study in patients with a bleeding event or in need of an emergency surgery resembles the situation of dabigatran treated patients and provides a so far limited dataset. The chosen placebo comparator was regarded as appropriate in the healthy volunteers' studies. In the case series study, where patients in emergency situations were treated with idarucizumab, a comparator arm was not included. It was agreed that this would have been unethical, and all standard of care treatments were allowed to be performed. The chosen endpoints to investigate the PK and PD of idarucizumab were considered appropriate. Further, the chosen endpoints and PD parameters to demonstrate the ability of idarucizumab to reverse the effect of dabigatran were also suitable. The conduct of the clinical development program was in line with the scientific advices obtained from the CHMP. The treatment compliance was very good.

Efficacy data and additional analyses

Data in healthy volunteers

The phase I programme included 283 healthy volunteers in three studies 1321.1, 1321.2, and 1321.5. The subjects reflect partially the planned patient population (elderly, renal impairment). Of these 117 received idarucizumab after pre-treatment with DE. 35 subjects were treated with the target clinical dose of 5 g idarucizumab. However, only 9 subjects (7.7%) were treated with the planned dose of 2 single infusions of 2.5g+2.5g idarucizumab given 15 min apart after DE intake. Of these, 6 subjects with moderate renal impairment were treated. Therefore, the experience with the proposed dosing regimen in healthy volunteers and in volunteers with renal impairment was considered to be very limited. In the pooled phase I data only 19 women were included in contrast to 264 male participants. Numbers of patients with mild or moderate renal impairment were also rather small (n=20) and limited the strength of the conclusions.

Results from the healthy volunteers studies revealed that administration of idarucizumab alone has **no effect on the measured clotting parameters** and did not show any hypercoagulative effect. The anticoagulant effect of dabigatran was reversed in a time and dose dependent manner. Doses >2g reversed the dabigatran effect completely and for a time period of at least 72h. All subjects in study 1321.2 treated with idarucizumab showed reversal of the dabigatran-induced prolongation of clotting time and none of the subjects (0%) receiving placebo showed reversal. Sustained reversal over the complete observation period depended on the dose: infusion of 2.5g and 5g idarucizumab resulted in sustained reversal of dabigatran-induced clotting time prolongation over the observation period of at least 24 h. No influence of sex, age, or renal impairment was shown.

Furthermore, the applicant provided data from study 1321.2 in a limited number of 6 healthy subjects to investigate the **possibility of re-treatment with idarucizumab** in a possible emergency situation. These data were regarded as very important. Although the number of cases was rather limited, it was demonstrated that re-exposure to idarucizumab resulted in comparable reversal of DE effect compared to the first exposure. Pre-treatment with DE and restart of DE treatment 24 h after infusion of placebo or idarucizumab to 12 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. The conclusion that **DE treatment can be reinstituted 24 h after the last dose of idarucizumab** can be drawn. Administration of another antithrombotic agent can be done at any time as idarucizumab is specific for dabigatran.

In the phase I studies 13% of the assessed subjects presented with **pre-existing unspecific antibodies** to the C-terminus of idarucizumab. These antibodies did not have any influence on the reversal effect of idarucizumab on clotting time prolongation after dabigatran use. 8% of subjects treated with idarucizumab developed **anti-drug antibodies** (ADA) with a maximum titer of 40. The applicant presented a "worst case scenario" showing that even subject with a titer of 40 will receive enough

idarucizumab with a 5g dose to overwhelm a possible ADA effect on efficacy. The CHMP agreed with this conclusion.

To conclude, the results from the **pooled dataset in healthy volunteers** from studies 1321.1, 1321.2, and 1321.5 demonstrated the complete reversal of the effect of DE treatment measured with the coagulation assays dTT, ECT, TT and aPTT for nearly all of the participating subjects. This data indicate that idarucizumab is able to reverse the effect of DE. However, some subjects did not gain a complete reversal. The applicant presented a conclusive reworking of the patient cases with **incomplete reversal**. The conclusions drawn were that incomplete reversal resulted from an individual patient's baseline above the pre-specified ULN for a specific assay. In exceptional cases incomplete reversal may result from a dabigatran body load that exceeds the binding capacity of 5 g idarucizumab. It was agreed that the rare case that dabigatran body load might exceed the binding capacity of idarucizumab could be managed with a second dose in case of clinical need.

The reversal effect of idarucizumab was seen very quickly with a median onset 5 minutes after the start of the infusion. This was considered by the CHMP very important for the clinical effect of the medicinal product. Mean duration of complete reversal for doses >2.5g was >50 hours and the median duration of complete reversal for dTT and ECT was 72h. This **duration of complete reversal** is long enough to fulfil the requirements of a reversal agent in an emergency situation like bleedings or emergency operations. For all the presented **subpopulations** regarding sex, age, underlying diseases and race, the numbers of assessed subjects was too small to draw a definite conclusion.

Data in patients

Phase 3 study 1321.3 (RE-VERSE AD) in patients taking DE was still ongoing (overall cut-off date for the second interim report (N=123): 1 April 2015, cut-off for central lab PK/PD data (N=90): 7 May 2015) at the time of the CHMP Opinion for idarucizumab. It was planned to treat in this study approximately 200 to 300 patients with a total dose of 5 g (two 2.5g vials) of idarucizumab. Patients taking DE were eligible for this study if they were ≥18 years at entry, signed the informed consent, and either had an overt bleeding which was judged by the physician to require a reversal agent (Group A) or were in a condition requiring emergency surgery or invasive procedure where adequate haemostasis was required (Group B).

The so far enrolled **elderly patients** (median age 77 years) represent the planned target population with expected concomitant diseases and medications, such as renal impairment, slight obesity, and cardiovascular problems. 117 patients were being treated with DE for atrial fibrillation, 2 for venous thromboembolism, and 4 for other indications.

All but one evaluable (baseline value above upper limit of normal for the respective marker (110% ULN) for the primary endpoint) patients showed **full reversal of anticoagulant effect** in the **primary endpoint marker dTT and ECT**. Results for the secondary markers aPTT and TT supported the results of the primary markers. The results of the measurement of unbound sum dabigatran clearly showed the reversal effect of idarucizumab on the dabigatran anticoagulant effect. It was noted that the known high variability of unbound sum dabigatran concentration at baseline, seem to have no effect on the efficacy of idarucizumab. The reversal of the anticoagulant effect of dabigatran by idarucizumab was demonstrated in this so far still limited patient population. The PK/PD data obtained are consistent with observations made in healthy volunteers in Phase I.

Reversal of elevated anticoagulation tests in dabigatran-treated patients was a **surrogate for clinical efficacy**. However, the clinical benefit of this reversal was depending very much on the individual patient clinical situation, disease or bleeding severity or location of the bleeding. It was noted that **bleeding stopped in 44 of 48 evaluable patients** within 72 hours and the median time to cessation of bleeding

was 9.8 hours. In the case of emergency surgery, **33 out of 36 evaluable patients had normal hemostasis during surgery**.

Two patients that are not included in the analysis of 123 patients received a **second dose of 5 g idarucizumab** due to re-bleeding. Results of these patients were presented and formed the, although very small, basis for the proposed statement on the possibility of re-treatment. There might be circumstances were patients with very high baseline dabigatran levels, recurrent bleeding or the need for a second surgical procedure have to be dosed with idarucizumab 5g a second time. Data of the presented two patients were regarded as supportive and a recommendation regarding additional dose of idarucizumab was added to the SmPC. The Applicant committed to further investigate administration of a second 5 g dose of idarucizumab as defined in the proposed SmPC in the ongoing RE-VERSE AD trial. The study protocol will be amended accordingly.

2.5.4. Conclusions on the clinical efficacy

The data in healthy volunteers were considered pivotal for the current application. The results of studies in healthy volunteers and in patients support that administration of idarucizumab in subjects exposed to DE leads to the reversal of the dabigatran anticoagulant effect. This effect starts very quickly already 5 minutes after administration and remains for at least 72 h in healthy volunteers and in patients with mild to moderate renal impairment (dose >2g). Reversal of elevated anticoagulation tests in dabigatran-treated patients was considered a surrogate for clinical efficacy. The clinical benefits of this reversal were depending very much on the individual patient situation, disease, bleeding severity or location of the bleeding. However, as there was no negative effect on patient's safety and administration of idarucizumab did not interfere with normal routine treatment of emergency patients presenting with bleeding or the need for surgery, the administration of idarucizumab was regarded as supportive for treatment of patients on DE when rapid reversal of its anticoagulant effects is required in emergency situations. Administration of idarucizumab alone did not show any effect on coagulation system of healthy volunteers. The efficacy of administration of idarucizumab with the proposed dose regimen of 2 times 2.5g was supported by the totality of the presented data in healthy volunteers as well as in treated patients.

2.6. Clinical safety

Patient exposure

The safety data base includes 283 healthy subjects in the three Phase I studies and 123 patients (66 patients with bleeding events (Group A) and 57 patients requiring surgery (Group B)).

Adverse events

Healthy volunteers (Phase I studies)

Table: Adverse event overall summary for the pooled Phase I studies during the treatment period

	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.

Frequency of subjects with AEs reported for at least 2 subjects in any treatment group on PT level during the treatment period, sorted by overall frequency in the Ida/DE+Ida group for the pooled Phase 1 studies - TS

		Placebo		Idarucizumab		Total	
	DE[1]	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)
Headache	11 (7.8)	2 (5.7)	0	9 (8.4)	3 (2.6)	2 (1.9)	12 (5.4)
Skin irritation	2 (1.4)	2 (5.7)	0	3 (2.8)	3 (2.6)	2 (1.9)	6 (2.7)
Dizziness	2 (1.4)	1 (2.9)	0	1 (0.9)	4 (3.4)	1 (1.0)	5 (2.2)
Back pain	1 (0.7)	1 (2.9)	1 (1.4)	4 (3.7)	0	2 (1.9)	4 (1.8)
Nasopharyngitis	0	1 (2.9)	1 (1.4)	2 (1.9)	1 (0.9)	2 (1.9)	3 (1.3)
Diarrhoea	4 (2.8)	0	1 (1.4)	2 (1.9)	1 (0.9)	1 (1.0)	3 (1.3)
Constipation	0	0	0	1 (0.9)	2 (1.7)	0	3 (1.3)
Fatigue	1 (0.7)	0	1 (1.4)	1 (0.9)	1 (0.9)	1 (1.0)	2 (0.9)
Pain in extremity	1 (0.7)	1 (2.9)	0	1 (0.9)	1 (0.9)	1 (1.0)	2 (0.9)
Injection site haematoma	0	0	1 (1.4)	1 (0.9)	1 (0.9)	1 (1.0)	2 (0.9)
Migraine	0	0	0	2 (1.9)	0	0	2 (0.9)
Musculoskeletal stiffness	0	0	0	2 (1.9)	0	0	2 (0.9)
Myalgia	1 (0.7)	0	0	1 (0.9)	1 (0.9)	0	2 (0.9)
Asthenia	1 (0.7)	0	0	0	2 (1.7)	0	2 (0.9)
Epistaxis	3 (2.1)	1 (2.9)	1 (1.4)	0	1 (0.9)	2 (1.9)	1 (0.4)
Nausea	4 (2.8)	0	1 (1.4)	1 (0.9)	0	1 (1.0)	1 (0.4)
Paraesthesia	2 (1.4)	0	0	0	1 (0.9)	0	1 (0.4)
Abdominal pain	3 (2.1)	0	0	1 (0.9)	0	0	1 (0.4)
Chest pain	0	1 (2.9)	1 (1.4)	0	0	2 (1.9)	0
Anxiety	2 (1.4)	0	1 (1.4)	0	0	1 (1.0)	0
Presyncope	5 (3.5)	0	0	0	0	0	0
Abdominal discomfort	4 (2.8)	0	0	0	0	0	0
Haematuria	3 (2.1)	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.

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. In healthy subjects there was no adverse event that was associated with idarucizumab more than with placebo or other comparison groups such as treatment with DE alone. However the numbers of subjects with events are too small to reach firm conclusions.

Headache was the most frequently reported AE, which was reported in the Ida alone group in 8.4% of the subjects. The only AEs to be reported more frequently in the Ida/DE+Ida groups compared to the placebo/DE+placebo groups were headache, migraine, skin irritation, dizziness, constipation, musculoskeletal stiffness, myalgia, asthenia, paraesthesia and abdominal pain. Of these, headache was also more frequent when only comparing the placebo alone group with the Ida alone group, 5.7% vs. 8.4%. There were two cases of migraine in the Ida alone vs none in the placebo alone group. One case of headache and one case of migraine were assessed by the investigator to be possibly drug-related.

The post-treatment period started 6 days after last intake of study medication. 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.

Adverse events related to bleeding were of special interest. Epistaxis occurred with higher frequencies in the DE pre-treatment (2.1%) and placebo/DE+placebo (1.9%) groups than in the idarucizumab /dabigatran+ idarucizumab 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 dabigatran+placebo group (1.4%) and for none of the idarucizumab-treated subjects. Injection site haematoma was reported with nearly identical frequencies in the placebo/dabigatran+placebo (1.0%) and idarucizumab /dabigatran+ idarucizumab (0.9%) groups.

Patients (Study 1321.3)

Table 3.1: 1 Adverse events 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
Source: Table 15.3.1.2: 1

The patients investigated in the Phase III trial overall were: having condition requiring thrombosis prophylaxis, were elderly and frequently had numerous comorbidities. They either had serious bleeding that needed intervention or another condition that required emergency surgery or other invasive procedure. This hampered the unbiased conclusion on the safety of idarucizumab.

Thrombotic events were reported in 5 patients, none of which were on antithrombotic therapy at the time of the event, and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. Mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established. Further adverse events, reported in greater than or equal to 5% of patients, were hypokalaemia (9/123; 7%), delirium (9/123; 7%), constipation (8/123; 7%), pyrexia (7/123; 6%), pneumonia (7/123; 6%).

Serious adverse event / deaths / other significant events

Healthy volunteers

There were no deaths, other SAEs, severe AEs, or other significant AEs as required to be reported according to the ICH E3 (ICH Guideline on the structure and content of the clinical study report) during the course of the study.

Patients (Study 1321.3)

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 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. The patient was not receiving antithrombotic therapy at the time of the event.

Mortality rate of intracranial haemorrhage patients is expected to be high. 24 patients in Group A presented with ICH as the qualifying event. Six of these cases were fatal, a rate of 25% mortality. In comparison there were 27 GI bleeds in Group A. Three of these patients died, a rate of 11.1%.

Thrombotic adverse events: There were 5 patients with thrombotic events during the study, 3 in Group A and 2 in group B.

Immunogenicity: Sampling for anti-drug antibodies (ADA) against idarucizumab in RE-VERSE AD was planned for pre-dose (Visit 1) and one or more post-dose samples (30± 7 days and 90±7 days, Visits 5 and 6, respectively). Data were available for 47 patients with a pre-dose sample and at least one post-dose sample. There are 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 d, possibly of mixed specificity. These data were very limited but indicated a low level of immunogenicity for idarucizumab, consistent with the levels of immunogenicity identified in the healthy volunteer population from Phase I. Measurement of ADA with two assays was planned. However, one assay was not performing as expected and the other anti-dabigatran assay (based on thrombin time) was sensitive to the presence of dabigatran. Previous exploration of the possible existence of anti-dabigatran antibodies was done in volunteers; at that time there was no convincing evidence of the immunogenicity of dabigatran bound to idarucizumab.

Laboratory findings

Healthy volunteers

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 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. 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.

Patients (Study 1321.3)

Laboratory data were consistent with the patient population entered into the study. The most consistently abnormal values were for activated partial thromboplastin time (aPTT) and serum creatinine. The latter is to be expected, given the high rate of renal dysfunction in these patients, and the former is elevated in patients anticoagulated with dabigatran. There was no detectable effect of idarucizumab on serum creatinine. 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. One patient had cholelithiasis and was to undergo urgent cholecystectomy. One patient was in renal and hepatic failure and required placement of a renal dialysis catheter. One patient had sepsis, renal failure and required placement of a deep vein catheter, an arterial line and a dialysis catheter. In all of these patients the elevations of the liver function tests could be attributed to the underlying conditions.

Safety in special populations

In patient study 1321.3 elderly patients with a high percentage of renal impairment were included. Decreased renal function was associated with a higher plasma concentration of dabigatran at baseline. Patients with poor renal function were also more likely to have some re-appearance of dabigatran at 12 or 24 hours after the dose of idarucizumab. However, no safety signals were observed.

Safety related to drug-drug interactions and other interactions

Idarucizumab was designed to specifically and tightly bind dabigatran and its active metabolites; thereby preventing dabigatran from binding thrombin and thus inhibiting its anticoagulant effect. Currently there are no known endogenous ligands, receptors, or other targets bound by idarucizumab. Classical drug-drug interaction via CYP 450 enzymes or drug transporter (such as P-glycoprotein) pathways are not expected and respective drug-drug interaction studies were not performed. Furthermore, because of its intravenous administration route, food is not expected to influence idarucizumab exposure.

Blood products such as packed red cells or fresh frozen plasma were used both before and after administration of idarucizumab. Approximately 68% of Group A patients and 40% of Group B patients received blood products before or after treatment with idarucizumab. However, since almost all patients showed complete reversibility and there were no safety issues, it was concluded that there were no relevant drug interactions with blood products.

There were many other baseline and concomitant medications in this patient population. Apart from the effect of antithrombotics on the clotting times, there was no apparent interaction that impacted safety. However, the numbers were small and there was no comparison group.

Discontinuation due to adverse events

None of the healthy subjects had AEs leading to discontinuation. There were no reported AEs in the 123 patients included in study 1321.3 that led to treatment discontinuation.

2.6.1. Discussion on clinical safety

The safety data base included **283 healthy subjects in three Phase I studies**. The volunteer subjects in these trials included 30 elderly subjects (65-80 years) and 20 subjects with mild (N=19) or moderate (N=1) renal impairment. Mean age of all subjects in these studies was 36 years. Only 6.7% (N=19) were female. Sixty-two subjects received doses of 5 g or more, with 35 subjects receiving the target clinical dose of 5 g exactly. The subgroups of elderly and renally impaired patients reflected the target population to some extent, although DE-treated patients typically would be frailer and have several co-morbidities. All of these subjects who received 5 g were pre-treated with DE. A comparable safety profile between the placebo/placebo + dabigatran groups and idarucizumab / idarucizumab + dabigatran groups were observed. There was no adverse event that was associated with idarucizumab more than with placebo or other comparison groups such as treatment with DE alone. However, the numbers of subjects with events were too small to reach firm conclusions. This is further evaluated in the ongoing study in patients.

In addition, the safety data of **123 patients treated in the clinical study RE-VERSE AD (1321.3)** were provided in the interim report of this study. These patients were elderly (median age 77 years, range 48 to 93 years), often with renal impairment (median CrCl 55.1 mL/min). Of the 123 patients treated with idarucizumab, 103 patients (83.7%) were reported with AEs during the treatment period. Of these 103 patients, 59 patients (89.4%) were in Group A (uncontrolled bleeding) and 44 patients (77.2%) in Group B (requiring surgery). There were **5 patients with thrombotic events** during the study, 3 in Group A and 2 in group B. Short narratives of these thromboembolic events were presented. The occurrence of thrombosis after intended reversal of the antithrombotic effect was not unexpected and not linked to the mode of action of idarucizumab. It was agreed to monitor further the occurrence of thromboembolic events in the post-marketing setting and thrombotic events were included as important potential risk in the agreed version of the RMP. Patients investigated in the Phase III trial overall required prophylaxis of thrombosis, were elderly and had numerous comorbidities. They either had serious bleeding that needed intervention or another condition that required emergency surgery or other invasive procedure. A statement regarding the **possibility of the re-initiation of the antithrombotic treatment** after idarucizumab administration was included in the SmPC.

Regarding the amount of **sorbitol of 2g** in one 50mg vial (4g of sorbitol with the planned target dose), it was agreed to add a warning regarding the use in hereditary fructose intolerance (HFI) patients in the SmPC. The addition of a warning rather than a contraindication for HFI patients was justified by referencing the emergency in which idarucizumab is used, which could outweigh the risks associated with administration. The applicant proposed not to contraindicate the use of idarucizumab in HFI patients for the following two reasons: (1) diagnosis of HFI in emergency situations is difficult (patients to be treated with idarucizumab are mostly critically ill, often in an emergency situation which may also include unconscious conditions. At the time of admission to hospital, relatives may be not available for further information on the patient's medical history, (2) a careful benefit-risk assessment of the treating physician on an individual patient level may result in a benefit for a treatment with idarucizumab. In such a situation, a contraindication may prevent a treating physician from the administration of idarucizumab which may put this patient on an increased risk for an unfavourable outcome. The CHMP agreed with this justification.

In the initial version of the RMP patients with HFI were included as an important identified risk however the PRAC agreed that the proposed routine risk minimization strategy was considered sufficient to manage the risk by informing the physicians about the additional care the patients need. With an appropriate warning in the product information, this risk was considered to be adequately managed and therefore inclusion in the RMP as an important identified risk was not warranted.

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2.6.2. Conclusions on the clinical safety

The safety data for idarucizumab showed an acceptable safety profile in 283 healthy volunteers and 123 emergency patients. There were **26 deaths** at the cut-off in the ongoing Phase III study, 13 each in bleeding and surgical patients. The CHMP agreed that the deaths were most likely related either to the index event or to co-morbidities. During the study, **5 patients developed thrombotic events**, all of them not on antithrombotic therapy. A statement regarding a possibility of the **re-initiation of the antithrombotic treatment** after idarucizumab administration was included in the SmPC. In the safety database, there were very **few AEs or SAEs**. All occurring adverse events were judged to be related to the index events or underlying diseases. The safety profile of the second interim analysis including 123 patients reflected the findings of the first interim analysis with 26 patients. In conclusion, the CHMP considered that safety profile of idarucizumab was favourable.

2.7. Risk Management Plan

The PRAC considered that the risk management plan version 1.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 2.0 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	Immunogenicity
	Hypersensitivity
	Thrombotic events
Missing information	Paediatric patients
	Pregnancy/breast-feeding
	Re-exposure to idarucizumab

Pharmacovigilance plan

Study/activity[1]	**Objectives**	**Safety concerns addressed**	**Status[2]**	**Date for submission of interim or final reports[3]**
Trial 1321.3 - A Phase III case series clinical study of the reversal of the anticoagulant effects of dabigatran by intravenous administration of 5.0 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures; category 3	To evaluate the reversal of the anticoagulant effects of dabigatran by i.v. administration of 5.0 g idarucizumab in patients treated with dabigatran etexilate who have uncontrolled bleeding or require emergency surgery or procedures	Immunogenicity, hypersensitivity, thrombotic events	Started	Final report Q1 2017

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risks		
Immunogenicity	Labelling in SmPC section 5.1, prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None
Hypersensitivity	Labelling in SmPC section 4.4, prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None
Thrombotic events	Labelling in SmPC sections 4.2 and 4.4, prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None

Missing information

Paediatric patients	Labelling in SmPC section 4.2, prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None
Pregnancy/breast-feeding	Labelling in SmPC section 4.6, prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required : (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None
Re-exposure to idarucizumab	Prescription only medicine, administration in hospital setting only by trained medical personnel, use by experienced emergency physicians in case a rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding).	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group with the following comments:

The QRD Group accepted the applicant's request to omit the following particulars on the vial label: statement of active substance and warning to keep away from children. The vials are to be stored inside the carton, which will be fully labelled.

The QRD Group requested that the excipients and the 'single-use' statement needed to be part of the vial label. The MAH details can be removed to gain space and the overall design of the label will need to be addressed. The abbreviation for the route of administration can also be used in case of space constraints.

In the frame of reviewing the readability of the mock-ups it was agreed that the list of excipients could also be omitted from the vial label.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Praxbind (idarucizumab) is included in the additional monitoring list as:

- it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- it is a biological product that is not covered by the previous category and authorised after 1 January 2011;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The effect of idarucizumab in reversing the anticoagulant effect of dabigatran has been shown in three pharmacokinetic (PK)/pharmacodynamics (PD) studies in 283 healthy subjects. The subjects were pre-treated with dabigatran etexilate (DE) in supratherapeutic doses for 3.5 days. Subsequent administration of idarucizumab reversed markers of dabigatran anticoagulant activity (dTT, ECT, aPTT and TT; 100% of subjects had complete reversal as assessed by the dTT assay and all but one subject [97.1%] had complete reversal based on the ECT assay) to levels similar to those seen before treatment with DE. This was in contrast to subjects who received placebo instead of idarucizumab.

Full reversal was observed in subjects receiving idarucizumab doses of 1 g or more and was evident in young and elderly subjects, in subjects with normal renal function as well as subjects with mild or

moderate renal impairment. There is very little experience with idarucizumab in patients with severe renal impairment and no experience from the Phase I studies.

The reversal of the anticoagulant effect was rapid and sustained. It was substantiated by low levels of unbound dabigatran in subjects receiving idarucizumab.

The results of the second interim analysis of the ongoing open label, uncontrolled, case series clinical study in patients (study RE-VERSE AD; 1321.3) treated with DE who were in actual need of rapid reversal of the anticoagulant activity largely confirmed the results of the PK/PD studies in healthy subjects with regards to reversed markers of dabigatran anticoagulant activity. However, the variability of this reversal was larger than in the PK/PD studies (>89% of patients achieved complete reversal as measured by dTT or ECT in the first 4 hours after administration of 5 g idarucizumab).

Restart of the anticoagulant treatment with DE after a bleeding event and idarucizumab administration could be initiated already 24 hours after last idarucizumab dose, if the patient is clinically stable and adequate hemostasis has been achieved. Furthermore, idarucizumab administration in the clinical study did not interfere with routine emergency patient management in case of bleeding or urgent surgery. Idarucizumab administration alone had no effect on coagulation parameters.

Uncertainty in the knowledge about the beneficial effects.

For all the presented subpopulations regarding sex, age, underlying diseases and race, the numbers of assessed subjects was still too small to draw final conclusions regarding possible differences in the beneficial effects.

The effect of idarucizumab therapy on reduction in morbidity or mortality (most notable bleeding complications) remained uncertain. The ongoing Phase III study (1321.3) was not powered nor designed to detect a difference between standard of care plus idarucizumab versus standard of care alone. However, this uncertainty was considered to be acceptable in view of the results of the non-clinical studies and since the PD biomarkers used in the PK/PD studies were considered to be good surrogates for efficacy. The results of the second interim analysis of the study 1321.3 supported the view that reversal of elevated anticoagulation tests in dabigatran-treated patients was a surrogate for clinical efficacy. However, the clinical benefit of this reversal was depending very much on the individual patient clinical situation, disease or bleeding severity or location of the bleeding.

Some patients may present with very high dabigatran exposure, for example patients taking an overdose with suicidal intention. Even though the proposed recommended idarucizumab dose of 5 g will be sufficient in most cases, a repeated dose may be appropriate in some situations. This is now reflected in the SmPC.

Risks

Unfavourable effects

The amount of sorbitol was very high with one target dose including 4 g of sorbitol. In patients with hereditary fructose intolerance (HFI), parenteral administration of sorbitol has been associated with reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function, and death. Therefore, in patients with HFI the risk of treatment with idarucizumab must be weighed against the potential benefit of such an emergency treatment. If idarucizumab is administered in these patients, intensified medical care during idarucizumab exposure and within 24 hours of exposure is required.

In the placebo-controlled PK/PD trials, there were few adverse events. Idarucizumab was not associated with any serious or severe adverse events. For some events, a causal relationship with idarucizumab was

considered by the CHMP, but it was not confirmed. These included headache, migraine, liver enzyme increases and redness at the infusion site. A dose-dependent, transient proteinuria was observed in subjects treated with idarucizumab. The reason was most likely related to the mechanism by which idarucizumab was excreted in the kidneys.

In the ongoing Phase III study in patients mild symptoms of potential hypersensitivity (pyrexia, bronchospasm, hyperventilation, rash or pruritus) were reported. A causal relationship to idarucizumab could not be established. Further adverse events, reported in greater than or equal to 5% of patients, were hypokalemia (9/123; 7%), delirium (9/123; 7%), constipation (8/123; 7%), pyrexia (7/123; 6%), pneumonia (7/123; 6%).

Anti-idarucizumab antibodies were detected in subjects treated with placebo and idarucizumab, and some had pre-existing antibodies. However, titers were generally low, and there were no suggestions that anti-idarucizumab antibodies diminished the efficacy to a clinically relevant degree.

In the ongoing Phase III study (RE-VERSE AD), 5 patient experienced thrombotic events following idarucizumab treatment. This was most likely not a direct effect of idarucizumab, but was caused by the lack of anticoagulant treatment.

Uncertainty in the knowledge about the unfavourable effects

The main uncertainty in the knowledge about unfavourable effects was the limited safety database rather than the results themselves. Safety data from placebo-controlled studies were solely derived from healthy subjects except for relatively few subjects with renal impairment, and not from a population typical of that treated with DE, i.e. old, frail patients with many co-morbidities. Safety data from placebo-controlled studies were complemented by interim data from the ongoing phase III study (open label, uncontrolled) in patients.

There was uncertainty about the safety and tolerability in patients with renal impairment as stated in the beneficial effects section. This uncertainly was related to the fact that: (i). the PK/PD studies included only subjects with normal or relatively modestly reduced renal function; (ii). a large proportion of the target population for DE has some degree of renal impairment; (iii). patients with major bleedings are likely to suffer from acute renal impairment; (iv). idarucizumab elimination is dependent on renal function.

Effects table

Effects Table for idarucizumab as an antidote for dabigatran (data cut-off: April 01, 2015).

Effect	Short Description	Unit	Idarucizumab	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects						
Reversal of dabigatran effect	Proportion of patients with a 100% reversal in coagulation marker values, dTT ECT (and TT aPTT) for those with baseline values above the 100% ULN threshold	%	Dose >2.5g: > 97%	 0%	Small number of subjects studied Supported by the interim data of phase III study in patients but variability of this reversal was larger than in the PK/PD studies Very limited data in patients with severe renal impairment	 Results of PK/PD studies in healthy volunteers

Effect	Short Description	Unit	Idarucizumab	Placebo	Uncertainties / Strength of evidence	References
Time to complete reversal	Median time	Minutes	5	N/A	Supported by the interim data of phase III study in patients	
Duration of reversal	Median duration	Hours	Dose >2,5g: 72	N/A	Supported by the interim data of phase III study in patients Possible re-elevation of clotting tests up to 2-24 h after administration of idarucizumab	
Unfavourable Effects						
Thrombotic events	Number of patients		5	N/A	Uncontrolled studies, therefore causality difficult to ascertain. Not considered to be direct effect of idarucizumab .	Interim data of phase III study in patients
Severe untoward reactions in patients with hereditary fructose intolerance (HFI) due to sorbitol content	[number of patients]		0	N/A	Small safety data-set, but as class effect there is theoretical risk of infusion and hypersensitivity reactions even though not observed in available studies	Sorbitol amount of 4g per dose

Abbreviations: dTT, Diluted thrombin time; ECT, Ecarin clotting time; TT, Thrombin time; aPTT, Activated partial thrombin time

Benefit-risk balance

Importance of favourable and unfavourable effects

In 3 PK/PD Phase I studies in healthy volunteers (including elderly and renally impaired subjects) and results of the interim analysis of the ongoing Phase III study in patients, 5 g of idarucizumab reversed the anticoagulant effect of dabigatran. This was shown with the coagulation test dTT, ECT, TT, and aPTT as well as the measurement of unbound sum dabigatran. The reversal started quickly only 5 minutes after administration of idarucizumab and lasted long enough to allow clinical emergency management of these patients.

The reversal of the anticoagulant effect of dabigatran by idarucizumab was demonstrated in a still limited population of 123 patients. The PK/PD data obtained in patients are consistent with observations made in healthy volunteers in Phase I studies.

The clinical events observed among the patients studied were often life-threatening and a high mortality rate was expected. The early findings regarding the clinical endpoints of bleeding reduction and minimal blood in operative field allowed the conclusion that patients may benefit from idarucizumab reversal of dabigatran-induced anticoagulation. The findings were however confounded by routine emergency care.

There was no indication of a pro-thrombotic effect of idarucizumab consistent with evaluations in healthy volunteers and with the preclinical data.

There is no evidence of worsening of the renal function when this drug was given to patients with renal impairment although numbers of patients were too small (particularly with severe renal impairment) to draw final conclusions. There is a high unmet medical need regarding the reversal agent for patients on direct oral anticoagulants and having life-threatening or uncontrolled bleeding or before emergency surgery/urgent procedures.

Idarucizumab was considered to have an acceptable safety profile. However, conclusions regarding this issue were hampered by the small population of patient treated so far and the underlying morbidity and co-morbidity of these patients. For patients with hereditary fructose intolerance administration of idarucizumab can lead to very severe side effects or even death.

Benefit-risk balance

Discussion on the benefit-risk balance

The data assessed within the current application supported that administration of idarucizumab in subjects exposed to DE lead to rapid reversal of the anticoagulant effect. This effect started already 5 minutes after administration of idarucizumab and was maintained for at least 72 h in healthy volunteers and in patients with mild to moderate renal impairment (dose >2g of idarucizumab).

The results of the second interim analysis of the Phase III study REVERSE-AD that included 123 patients support the results of the PK/PD studies in healthy volunteers and confirm that the reversal of prolonged clotting times in dabigatran-treated patients could be a surrogate for clinical efficacy. However, the clinical benefit of this reversal depends very much on the clinical status of the individual patient, the severity of the disease/bleeding or location of the bleeding. The results of this ongoing Phase III study will be submitted for the assessment as per pharmacovigilance plan agreed in the RMP and should permit for further confirmation of the efficacy of idarucizumab in reversing the anticoagulant effect of DE and the safety of this medicinal product by addressing important potential risks (immunogenicity, hypersensitivity and thrombotic events).

Following the administration of idarucizumab, there were no reported adverse events observed in studies so far where a causal relationship to idarucizumab was evident. Its administration did not interfere with routine treatment applied in case of emergent bleeding or urgent surgery. The administration of idarucizumab was regarded as supportive in these situations.

The efficacy of idarucizumab with the proposed dose regimen of 2 times 2.5 g intravenously was supported by the totality of the presented data in healthy volunteers as well as in treated patients.

The favourable effects of complete reversal of the anticoagulant effect of dabigatran in combination with a supportive safety profile of the medicinal product lead to the CHMP conclusion on a positive benefit-risk balance.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of idarucizumab, a specific reversal agent for dabigatran and indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required:

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

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that idarucizumab is qualified as a new active substance.