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APPLICATION NUMBER:

761025Orig1s000

<u>MEDICAL REVIEW(S)</u>

CLINICAL REVIEW

Application Type	New BLA
Application Number(s)	761025
Priority or Standard	Priority
Submit Date(s)	February 19, 2015
Received Date(s)	February 19, 2015
PDUFA Goal Date	October 19, 2015
Division/Office	Division of Hematology Products
Reviewer Name(s)	Andrew Dmytrijuk, M.D.
Review Completion Date	August 10, 2015
Established Name	Idarucizumab
(Proposed) Trade Name	Praxbind
Applicant	Boehringer Ingelheim Pharmaceuticals 900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877
Formulation(s)	Humanized Monoclonal Antibody Fragment For Intravenous Infusion
Dosing Regimen	Two 2.5 mg Intravenous Infusions (b) (4)
Applicant Proposed Indication(s)/Population(s)	Patients Treated With Dabigatran (Pradaxa®) When Rapid Reversal Of The Anticoagulant Effect Of Dabigatran Is Required For Emergency Surgery/Urgent Procedures Or In Life Threatening or Uncontrolled Bleeding
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients Treated With Dabigatran (Pradaxa®) When Rapid Reversal Of The Pharmacodynamic Effects Of Dabigatran Is Required For Emergency Surgery/Urgent Procedures Or In Life Threatening or Uncontrolled Bleeding

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Glossary

AC   advisory committee
ACT   activated clotting time
AE   adverse event
aPTT   activated partial thromboplastin time
BLA   biologics license application
BPCA   Best Pharmaceuticals for Children Act
BRF   Benefit Risk Framework
CBER   Center for Biologics Evaluation and Research
CBC   Complete Blood Count
CDER   Center for Drug Evaluation and Research
CDRH   Center for Devices and Radiological Health
CDTL   Cross-Discipline Team Leader
CFR   Code of Federal Regulations
CMC   chemistry, manufacturing, and controls
COSTART   Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF   case report form
CRO   contract research organization
CRT   clinical review template
CSR   clinical study report
CSS   Controlled Substance Staff
DMC   data monitoring committee
dTT   dilute thrombin time
ECG   electrocardiogram
ECT   ecarin clotting time
eCTD   electronic common technical document

ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBO	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TT	thrombin time

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1 Executive Summary

1.1. Product Introduction

BLA 761025 supporting document 2 letter date February 19, 2015 for Praxbind® (idarucizumab, BI 655075) should be granted accelerated approval from a clinical perspective. The sponsor's proposed indication is as follows.

- Praxbind® (idarucizumab) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (Pradaxa®) when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

However, the proposed indication should be changed to remove the wording, "anticoagulant effect" and replaced with the wording "pharmacodynamic effect" which more accurately reflects that the demonstrated effect of idarucizumab in clinical trials is on pharmacodynamic clotting parameters. Therefore, the idarucizumab indication should read as follows and incorporate the recommendations of reviewers as shown in Section 10.2 Patient Labeling in this review.

- Praxbind® (idarucizumab) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (Pradaxa®) when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The sponsor has provided substantial evidence to support the approval of idarucizumab from two phase 1 pharmacokinetic and pharmacodynamic studies which demonstrated that idarucizumab is able to reverse the pharmacodynamic effects of dabigatran, based on coagulation tests, in adult normal healthy volunteers at steady state. Support for this conclusion is demonstrated in two phase 1 studies (studies 1321.1 and 1321.2 described in detail below in section 4.5 Clinical Pharmacology). These were randomized, placebo controlled, double-blind, studies in which dabigatran 220mg was administered orally twice daily for 3 days with an additional 220mg dose administered on day 4 followed by single or divided intravenous

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idarucizumab infusions of up to 8g. These studies demonstrated that there was a dose dependent reversal of the pharmacodynamic effect of dabigatran by idarucizumab in normal healthy volunteers who received intravenous single or split doses of idarucizumab ranging from 20mg to 8g administered over up to 1 hour or two 2.5g infusions over 5 minutes up to 1 hour apart following dabigatran administration. From a clinical perspective, the reversal of the pharmacodynamic effect of dabigatran by idarucizumab was established using several different coagulation tests, e.g., dilute thrombin time (dTT), thrombin time (TT), ecarin clotting time (ECT) and activated partial thromboplastic time (aPTT). In these two studies 159 subjects were exposed to idarucizumab. Additional supportive safety and efficacy data comes from an ongoing phase 3 (study 1321.3 described in detail below (see the Review of Relevant Individual Trials Used to Support Efficacy) which has enrolled 123 adult patients who are being treated with dabigatran and require emergency surgery or procedures for other morbidities or are being treated with dabigatran and present with life-threatening or uncontrolled bleeding. Data from this interim analysis demonstrates that administration of two doses of idarucizumab 2.5 mg intravenously (b) (4) can rapidly reverse and sustain the reversal of the pharmacodynamic anticoagulant effect of dabigatran for at least 24 hours after the last administration of idarucizumab.

The Clinical Pharmacology Review by Dr. Martina Shahre, final signature date August 10, 2015 states that the Office of Clinical Pharmacology has determined that, pending the inspection results for one of the analytical sites and labeling agreement, there is sufficient clinical pharmacology information provided in the NDA to support approval of idarucizumab for the rapid reversal of the anticoagulant activity of dabigatran in emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding. The Clinical Pharmacology Review States that Administration of 5 g of idarucizumab at steady-state exposures of dabigatran causes an immediate decrease of unbound dabigatran concentrations in most patients. Coagulation markers, e.g., dilute thrombin time (dTT), thrombin time (TT), and activated partial thromboplastic time (aPTT) follow the pharmacokinetics of unbound dabigatran closely and thereby lead to immediate reversal of dabigatran mediated anticoagulant activity.

The sponsor requests waiver of the requirement for pediatric studies in 21 CFR Section 314.55(a). Dabigatran is not approved in pediatric patients in the US. The sponsor states idarucizumab is not likely to be used in a substantial number of pediatric patients treated with dabigatran who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required. The sponsor should complete study 1321.3 and submit a final study report as a Post Marketing Requirement (PMR) to support the application's approval. Completion and submission of final study results for study 1321.3 will allow identification and assessment of any unexpected serious risk related to the use of idarucizumab in patients treated with dabigatran when rapid reversal of the anticoagulant pharmacodynamic effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

1.3. Benefit-Risk Assessment

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Benefit-Risk Summary and Assessment

In two studies in normal healthy volunteers (studies 1321.1 and 1321.2) treated with dabigatran 220mg orally twice daily for 3 days followed by one 220mg dose on day 4 a rapid, dose dependent, reversal of the dabigatran pharmacodynamic effect was observed within 30 minutes of the administration of idarucizumab at doses ranging from 20mg to 8g administered over up to 1 hour or two 2.5g infusions over 5 minutes up to 1 hour apart. The sponsor determined that a 5 g dose or two 2.5 g doses of idarucizumab were the lowest doses of idarucizumab that would be able to neutralize dabigatran for a projected 99% of patients with moderate renal failure from the RE-LY trial, i.e., the pivotal trial used to support the initial marketing application approval for dabigatran. Based on a population pharmacokinetic (PK) model of data from RE-LY the 99th percentiles of trough and peak concentrations of dabigatran in patients with moderate renal failure were 543 and 861 ng/mL. In an interim analysis of an ongoing study (1321.3) in patients who are being treated with dabigatran and require reversal of the dabigatran pharmacodynamic effect due to serious bleeding or the requirement for urgent surgery or procedures idarucizumab administered as two 2.5g intravenous infusions separated by 15 minutes or as a single bolus was able to reverse the pharmacodynamic effect of dabigatran.   The reversal of the pharmacodynamic effect by idarucizumab was established using several different coagulation tests such as dilute thrombin time (dTT), thrombin time (TT), ecarin clotting time (ECT), activated partial thromboplastin time (aPTT) and activated clotting time (ACT). This pharmacodynamic reversal effect was sustained for a period of at least 24 hours after the last dose of idarucizumab. A dose of 5 g of idarucizumab was calculated by the sponsor to be sufficient for full reversal of dabigatran anticoagulant effect in 99% of patients, based on dabigatran plasma concentrations observed in previous studies of dabigatran used to support its marketing approval. The complete dose of 5 g is administered intravenously as two consecutive infusions over 5 to 10 minutes. The reversal of elevated anticoagulation tests in dabigatran-treated patients is a surrogate for clinical efficacy. The coagulation tests, e.g., aPTT, dTT, pre- and post-treatment, may help the treating physician determine whether reversal of dabigatran has occurred. The data from studies 1321.1 and 1321.2 document the pharmacologic effect and in these normal healthy volunteer studies there were no discontinuations due to adverse events (AEs) and no serious adverse (SAEs). AEs that were observed were of mild-moderate severity. Similarly data from study 1321.3 supports the idarucizumab reversal of the pharmacodynamic anti-coagulant effect of dabigatran in the target population, i.e., when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. In This study among 123 patients treated with idarucizumab adverse events appeared to be unrelated to treatment. In this study 26 patients died primarily due to complications related to their serious medical conditions, i.e., serious bleeding or causes for the need for urgent surgery/procedures, e.g., trauma or abdominal surgery. The mortality rate was not unexpected in a high risk population with life-threatening events. Two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. There is no evidence of worsening renal function when idarucizumab is given to patients with renal impairment and full efficacy is

maintained.

The clinical outcome, i.e., a decrease in the risk of bleeding, is difficult to assess. In many cases, bleeding is not visible and cannot be readily measured, e.g. in patients with intracranial hemorrhage (ICH). Other clinical outcomes such as mortality are also significantly confounded by the severity of the underlying clinical situation, e.g., trauma or duration and complications of surgery. A control group to compare outcomes would not be ethical to determine whether mortality rates are impacted by administration of idarucizumab. The target patient population is dabigatran treated patients who require emergency surgery or other invasive intervention where anticoagulation may increase the risk of bleeding, and dabigatran treated patients with life-threatening or uncontrolled bleeding requiring urgent intervention. The sponsor estimates that the incidence of these conditions based on observations in the pivotal trials for dabigatran that the major bleeding rate for patients treated with dabigatran is approximately 3% and is estimated by the sponsor to be <2.5% per year for life-threatening or uncontrolled bleeding during or emergency surgery. Idarucizumab is not intended for use in patients with minor bleeding or other bleeding where standard supportive care is sufficient. It is expected that usage of this drug would be confined to Emergency Departments or other critical care facilities. In summary, 5 g of idarucizumab (administered as 2, 2.5 g infusions separated by 15 minutes) appears to be safe and effective in the reversal of dabigatran anticoagulant pharmacodynamic effect in patients treated with dabigatran who require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. The sponsor should complete study 1321.3 in order to support the approval of idarucizumab for this indication.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Patients treated with dabigatran who require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. Two clinical pharmacology studies (1321.1 and 1321.2) demonstrate that in normal healthy volunteers pre-treated with dabigatran treatment with idarucizumab decreases the pharmacodynamic anticoagulant effect of dabigatran as demonstrated by coagulation tests such as aPTT, TT, dTT. Idarucizumab is a drug specifically targeted to dabigatran which reverses the dabigatran pharmacodynamic effect. It is not targeted	As with all anticoagulants, patients treated with dabigatran, may be at increased risk for bleeding. Studies 1321.1 and 1321.3 demonstrate that idarucizumab is able to reverse the pharmacodynamic anticoagulant effect of dabigatran. Reversal of the anticoagulant effect of dabigatran is an important clinical benefit in order to decrease the risk of bleeding in patients who may

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	against any other anticoagulant and it is not designed to reverse the pharmacodynamic effect of any other anticoagulant.	require emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding.
Current Treatment Options	• Currently there are no approved therapies for the reversal of the anticoagulant effect of dabigatran. The dabigatran product label states that the half-life of dabigatran in healthy subjects is 12 to 17 hours. Recommendations for patients who bleed while receiving dabigatran are based on the mechanism of action of dabigatran, i.e., to administer agents that may possibly overwhelm the inhibited coagulation cascade. Administration of activated prothrombin complex concentrates (PCCs, e.g. FEIBA) or recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X could be considered, however, these agents have their effects at points in the cascade prior to thrombin. Other, management approaches that could be considered include supportive care with blood products such as fresh frozen plasma, fresh or packed red blood cell (RBCs) transfusions or packed platelet transfusions. However, even with these agents thrombin is a critical factor for coagulation. Dabigatran can be hemodialyzed out of a patient's circulation. Approximately 60% of the drug can be removed over 2-3 hours. (Hankey, G. J. and Eikelboom, J.W.: Dabigatran: a new oral thrombin inhibitor. 2011. Circulation. 123:1436-1450) However, this approach may not be optimal in a situation that requires rapid anticoagulant reversal.	Idarucizumab is an antidote for dabigatran. Idarucizumab directly binds to dabigatran and reverses dabigatran's pharmacodynamic anticoagulant effect.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Two clinical pharmacology studies (1321.1 and 1321.2) demonstrate that in normal healthy volunteers pre-treated with dabigatran that treatment with idarucizumab decreases the pharmacodynamic anticoagulant effect of dabigatran as demonstrated by coagulation tests such as aPTT, TT, dTT. Additional support for these results comes from one ongoing phase 3 study (1321.3) in patients who are being treated with dabigatran and require reversal of the dabigatran pharmacodynamic effect due to requirement of emergency surgery or other invasive procedure or who present with life-threatening or uncontrolled bleeding. This study is an open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to adult 300 patients.	The phase 3 study is ongoing. To date 123 of a planned 300 patients have been enrolled. A decrease in the risk of bleeding is difficult to assess. In many cases, bleeding is not visible and cannot be readily measured, e.g. in patients with intracranial hemorrhage (ICH). Other clinical outcomes such as mortality are also significantly confounded by the severity of the underlying clinical situation, e.g., trauma or duration and complications of surgery. A control group to compare outcomes would not be ethical to determine whether mortality rates are impacted by administration of idarucizumab. The target patient population is dabigatran treated patients who require emergency surgery or other invasive intervention where anticoagulation may increase the risk of bleeding, and dabigatran treated patients with life-threatening or uncontrolled bleeds that require urgent intervention.
Risk	• The data from studies 1321.1 and 1321.2 document the pharmacologic effect and in these normal healthy volunteer studies there were no discontinuations due to adverse events (AEs) and no serious adverse (SAEs). AEs that were observed were of mild to moderate severity. Similarly data from study 1321.3 supports the	Study 12321.3 is ongoing. The safety database in patients that have been treated with dabigatran is relatively small, i.e., 123 patients have been treated in study 1321.3 out of a planned 300 patients to be enrolled.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	idarucizumab reversal of the pharmacodynamic anti-coagulant effect of dabigatran in the target population, i.e., when rapid reversal of the pharmacodynamic effects of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. In 123 patients treated with idarucizumab adverse events appeared to be unrelated to treatment. In this study 26 patients died due to their underlying serious medical conditions. The mortality rate was not unexpected in a high risk population with life-threatening events. Two patients developed thrombotic events, these occurred 9 and 13 days after treatment with idarucizumab and in the absence of any antithrombotic treatment. There is no evidence of worsening renal function when this drug is given to patients with renal impairment and full efficacy is maintained.	
Risk Management	• Idarucizumab is a targeted antidote for dabigatran.	The sponsor should complete study 1321.3 in order to support the approval of idarucizumab and to enhance the idarucizumab safety database. The purpose for this study is to demonstrate the efficacy and safety of idarucizumab for the reversal of the pharmacodynamic effects of dabigatran in patients who require an urgent surgical procedure or who have serious bleeding. No additional Risk Management Plans are recommended at this time.

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2 Therapeutic Context

2.1. Analysis of Condition

Idarucizumab is a humanized antigen-binding fragment (Fab) against the direct thrombin inhibitor dabigatran. The proposed indication for idarucizumab is as follows.

- Praxbind® (idarucizumab) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (Pradaxa®) when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

Dabigatran was approved for marketing on October 19, 2010. Dabigatran is approved for the following indications.

- To reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days.
- To reduce the risk of recurrence of DVT and PE in patients who have been previously treated.

The recommended dose of dabigatran ranges from 75mg orally twice daily to 150mg orally twice daily and depends on the indication for which dabigatran is prescribed and the patient's creatinine clearance (CrCl), e.g., for the treatment of deep vein thrombosis (DVT) or for the reduction in risk of stroke and systemic embolism in non-valvular atrial fibrillation in a patient with CrCl >30mL/min the recommended dose is 150mg orally twice daily. However, if the CrCl is < 30mL/min in these patients the recommended dose of dabigatran is 75mg orally twice daily for the reduction in risk of stroke indication. Dosing recommendations for dabigatran in patients with DVT and CrCl <30mL/min are not provided in the dabigatran product label.

The target patient population for idarucizumab is dabigatran treated patients who require emergency surgery or other invasive intervention where anticoagulation may increase the risk of bleeding, and dabigatran treated patients with life-threatening or uncontrolled bleeds that require urgent intervention. The sponsor estimates that the incidence of these conditions based on observations in the pivotal trials for dabigatran that the major bleeding rate for patients treated with dabigatran is approximately 3%, and is estimated by the sponsor to be <2.5% per year for life-threatening or uncontrolled bleeding during or emergency surgery.

2.2. Current Treatment Options

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The Warnings and Precaution section of the dabigatran product labels states that serious and fatal bleeding can occur in patients who are treated with dabigatran. Currently there are no approved therapies for the reversal of the anticoagulant effect of dabigatran. In clinical practice guidelines recommendations for patients who bleed while receiving dabigatran are based on the mechanism of action of dabigatran, i.e., to administer agents that may possibly overwhelm the inhibited coagulation cascade. (Van Ryn, 2010) Administration of activated prothrombin complex concentrates (PCCs, e.g. FEIBA) or recombinant Factor VIIa, or concentrates of coagulation factors II, IX, or X could be considered, however, these agents have their effects at points in the clotting cascade prior to thrombin. (Eerenberg, 2011) Other, management approaches that could be considered include supportive care with blood products such as fresh frozen plasma, fresh or packed red blood cell (RBCs) transfusions or packed platelet transfusions. However, even with these agents thrombin is a critical factor for coagulation. Dabigatran can be hemodialyzed out of a patient's circulation. Approximately 60% of the drug can be removed over 2-3 hours. (Hankey and Eikelboom, 2011) However, this approach may not be optimal in a situation that requires rapid anticoagulant reversal.

Reviewer comment for section 2. Idarucizumab is a humanized antigen-binding fragment (Fab) against the direct thrombin inhibitor dabigatran developed for the treatment of patients treated with dabigatran when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. Currently available treatment options for these patients are mainly supportive such as transfusions of RBCs and platelets. Other treatment options such as PCC, other blood products, dialysis have their effects at points in the clotting cascade prior to thrombin or the effects may not be sufficiently rapid in an emergency bleeding situation.

3   Regulatory Background

3.1.   U.S. Regulatory Actions and Marketing History

Idarucizumab is not currently marketed in the United States.

3.2.   Summary of Presubmission/Submission Regulatory Activity

- Pre-IND meetings were held on August 10, 2011, January 31, 2013 and February 11, 2014 under IND 112278. The original interactions involved the Division of Cardiovascular and Renal Products (DCRP), because at the time of development of idarucizumab (BI 655075), the only approved indication for dabigatran, an oral direct thrombin inhibitor, was for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. DCRP consulted the Division of Hematology Products (DHP) when the original submission was made. In the discussions between the

two Divisions, there appeared to be a difference of opinion regarding the types of studies that were needed to provide data for the efficacy and safety of the use of idarucizumab that would support approval of the drug and the indication for which it might be approved (see IND 112278 Meeting Minutes dated August 30, 2011; Clinical Review by Dr. George Shashaty final signature date January 25, 2013 and Meeting Minutes dated February 6, 2014).   The key discussion points were as follows.

- o To support a labeled indication a study evaluating clinical outcomes in bleeding patients may be required.
- o The surrogate pharmacodynamic endpoint, e.g., aPTT, should be associated with cessation of bleeding and/or other clinical benefits.
- o There may be increased risk for adverse reactions, e.g., thrombosis, after administration of idarucizumab (BI 655075) due to the underlying diseases/conditions that required the use of the anticoagulant dabigatran.

However, the Divisions have come to a consensus agreement that pharmacodynamic assessments (clotting assays) along with pharmacokinetic data and additional clinical outcomes that may be available, would be acceptable to support the assessment of the efficacy and safety of the drug.

- Breakthrough Therapy Designation Request submitted in IND 112278 for idarucizumab on April 17, 2014 for the proposed indication for patients treated with dabigatran when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.
- June 16, 2014 Breakthrough Therapy Designation granted.
- The applicant orientation meeting was held on April 13, 2015.

3.3.   Foreign Regulatory Actions and Marketing History

Idarucizumab is has not been approved or marketed outside the US.

Reviewer comment for section 3. Idarucizumab is not marketed anywhere in the world. Idarucizumab was granted Breakthrough Therapy Designation on June 16, 2014.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1.   Office of Scientific Investigations (OSI)

An Office of Translational Sciences Review was completed by Dr. Shila Nkah final signature date

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June 12, 2015. In her review Dr. Nkah recommends accepting data without an on-site inspection because the Office of Translational Sciences recently inspected SGS Life Science Services Clinical Research Clinical Pharmacology Unit and the inspectional outcome from the inspection was classified as No Action Indicated (NAI). The Office of Translational Sciences recently inspected _____ (b) (4) and the inspectional outcome from the analytical site was classified as Voluntary Action Indicated (VAI). Although, the last inspection was classified as a VAI, based on the nature of the findings from our last inspection, and the recommendation to the review division, an inspection of the site will not be needed at this time.

4.2.   Product Quality

The Chemistry, Manufacturing and Controls (CMC) review is ongoing. No significant product quality issues have been identified from a clinical perspective.

4.3.   Clinical Microbiology

The Clinical Microbiology review is ongoing. No significant Clinical Microbiology issues have been identified from a clinical perspective.

4.4.   Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review of the idarucizumab application completed by Dr. Emily Place final signature date July 20, 2015 states that pharmacology/toxicology studies conducted support approval of idarucizumab for the proposed indication, i.e., patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. Dr. Place states in her review that three animal models of activity were submitted in support of the application: a mouse intracranial hemorrhage model; a rat tail cut bleeding model, and a pig blunt liver trauma model. All 3 animal pharmacology models showed the effectiveness of the neutralization activity of idarucizumab, and its ability to significantly reduce anticoagulation and blood loss. Safety pharmacology studies showed no adverse respiratory findings. Cardiovascular safety pharmacology studies were not performed independently but electrocardiogram (ECG) measurements assessed during the 2 week repeat dose toxicology study in monkeys were unremarkable at doses up to 500 mg/kg.

4.5.   Clinical Pharmacology

4.5.1. Mechanism of Action

Idarucizumab is a humanized Fab fragment that was developed as a dabigatran reversal agent. Dabigatran is a direct thrombin inhibitor anticoagulant. By binding dabigatran that would otherwise bind to thrombin, the anticoagulant effect of dabigatran is reversed by idarucizumab.

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The Clinical Pharmacology Review was completed by Dr. Martina Sahre (Clinical Pharmacology Reviewer, final signature date August 10, 2015). In her review Dr. Sahre states that *In vitro* studies show that idarucizumab binds to dabigatran with high affinity. The association (ka) and dissociation (kd) rate constants are $3.4x\ 10^5\ M^{-1}s^{-1}$ and $0.7x\ 10^{-6}s^{-1}$, respectively.

4.5.2. Pharmacodynamics

The sponsor conducted three clinical pharmacology studies, i.e., 1321.1, 1321.2 and 1321.5 to support the safety and efficacy of idarucizumab for the proposed indication. In addition the sponsor provided additional supportive safety and efficacy data from the ongoing study 1321.3. These studies are discussed in detail in section 6 Review of Relevant Individual Trials Used to Support Efficacy.

Dr. Sahre states in her review that idarucizumab has no intrinsic pro-thrombotic effect as shown by its lack of effect on coagulation markers or on the endogenous thrombin potential. Administration of 5 g of idarucizumab at steady-state exposures of dabigatran causes an immediate decrease of unbound dabigatran concentrations in most patients. Coagulation markers ECT, aPTT, TT, and dTT follow the pharmacokinetics of unbound dabigatran closely, thereby leading to immediate reversal of dabigatran mediated anticoagulant activity in most of the patients. Dabigatran redistribution peaks between 2.3- 18.4 ng/mL were observed in all subjects (n=26) that received the 5 g dose in study 1321.2. The peaks occurred approximately 24 hours following idarucizumab administration. One subject had a distribution peak of 46 ng/mL. Re-initiation of dabigatran treatment 24 hours after treatment with idarucizumab results in comparable unbound sum dabigatran concentrations and anticoagulant activity before and after idarucizumab treatment.

4.5.3. Pharmacokinetics

Dr. Sahre states in her review Idarucizumab disposition is dominated by the rapid initial distribution half-life of around 45 min. Idarucizumab declines to less than 20% of its peak concentrations 2 h after administration. Idarucizumab displayed dose-linear kinetics for doses ranging from 20 mg to 8 g. Age (20 to 76 years), sex, and race (Asians vs. Whites) did not influence idarucizumab disposition in a clinically relevant manner. When administered to patients with mild and moderate renal impairment, idarucizumab exposure (AUC) increased by 40% and 80%, respectively. Given that dabigatran exposure also increases with renal impairment, no dose adjustment is necessary for mild or moderate renal impairment as the effects of exposure increase for both idarucizumab and dabigatran go in the same direction. Idarucizumab does not distribute extensively to peripheral tissues. Its volume of distribution is estimated to be 5 – 8 L, suggesting that idarucizumab is mainly present in interstitial fluid.

4.6. Devices and Companion Diagnostic Issues

Clinical Review
Andrew Dmytrijuk, M.D.
BLA 761025
Praxbind (Idarucizumab)

No devices or companion diagnostics were developed with idarucizumab.

4.7.   Consumer Study Reviews

During the Late Cycle Meeting held with the sponsor on July 27, 2015 (see Late Cycle Meeting Minutes by Alycia Andersen, Project Manager, final signature date August 5, 2015) the Division of Medication Errors Prevention and Analysis (DMEPA) stated the recommended dose of idarucizumab is 5 grams, provided in two vials, each containing 2.5 gm/50 mL. From a medication error standpoint, we are concerned that healthcare practitioners may not administer the entire dose as packaged due to the fact that one dose is comprised of two separate vials. Therefore, underdoses may occur. The applicant should provide a rationale for the current packaging of two 2.5 gram vials instead of a one 5 gram vial. During the meeting the sponsor stated that they would work on submitting a response to this information request.

Reviewer comment for section 4. The OSIS review recommends accepting data in BLA 761025 without an on-site inspection because OSIS recently inspected SGS Life Science Services Clinical Research Clinical Pharmacology Unit and the inspectional outcome from the inspection was classified as NAI. I agree with the OSIS recommendation. No CMC or Clinical Microbiology issues have been identified, however these reviews are ongoing. The Pharmacology/Toxicology review states that pharmacology/toxicology studies conducted support approval of idarucizumab for the proposed indication, i.e., patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. The Clinical Pharmacology Review states that there is sufficient clinical pharmacology information provided in the NDA to support approval of idarucizumab for the rapid reversal of the anticoagulant activity of dabigatran in emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding. I agree with the Clinical Pharmacology recommendation. The Clinical Pharmacology Review also states that the idarucizumab label should include a warning that elevated coagulation parameters will occur in some patients (due to redistribution of dabigatran) with the proposed 5 g idarucizumab dose. I agree with the Clinical Pharmacology recommendation and the additional proposed wording to be added to the idarucizumab product label that elevated coagulation parameters will occur in some patients (due to redistribution of dabigatran) with the proposed 5g idarucizumab dose.

5 Sources of Clinical Data and Review Strategy

5.1.   Table of Clinical Studies

The sponsor's tables below show the studies used to support the application.

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Table 1. Table of 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 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

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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
PK, PD	1321.3 [c03124096]	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	26 (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:

bid: 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.

Sponsor's tables Tabular Listing of Studies pages 1-4

5.2. **Review Strategy**

All the studies, with exception of study 1321.3, were conducted in normal healthy adult volunteers. Studies 1321.1, 1321.2 were the pivotal studies used to support the idarucizumab application.   Study 1321.5 was considered to supportive of the clinical pharmacology data. Study 1321.3 is an ongoing prospective, open-label, nonrandomized, uncontrolled, observational study in which 123 adult patients, treated with dabigatran who required rapid

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reversal of the anticoagulant effect of dabigatran for emergency surgery/urgent procedures or life threatening or uncontrolled bleeding, were enrolled from June 2014 until April 1, 2015. An interim report of the results from study 1321.3 was submitted by the sponsor in BLA 761025 supporting document 13 letter date June 19, 2015 and the results of this interim report are considered supportive of the safety and efficacy of idarucizumab.

Reviewer comment for section 5. The Clinical Pharmacology Reviewer's important conclusions regarding studies 1321.1, 1321.2, 1321.5 and 1321.3 from a clinical perspective are summarized in section 4.5 Clinical Pharmacology in this review. My clinical review of these studies is discussed in section 7 Review of Effectiveness and section 8 Review of Safety.

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. Studies 1321.1, 1321.2 and 1321.3

Study 1321.1 is titled, "Randomized, Double-Blind, Placebo Controlled, Phase 1 Study in Healthy Male Volunteers to Investigate Safety, Tolerability and Pharmacokinetics of Single Rising Doses of BI 655075 (Idarucizumab) and to Explore the Dose of BI 655075 Effective to Reverse Dabigatran Anticoagulant Activity". In part 1 of this study single doses of placebo (PBO) or idarucizumab were administered at doses ranging from 20mg to 8 g over 1 hour or 1g to 4g over 5 minutes. One hundred ten subjects were treated (83 subjects treated with idarucizumab and 27 subjects treated with placebo). In part 2 of the study, subjects received dabigatran 220mg orally twice daily for 3 days and an additional 220mg dose on day 4 followed by PBO or idarucizumab administered at doses of 1g to 4 g intravenously over 5 minutes. Thirty five subjects were treated (26 subjects treated with idarucizumab and 9 subjects treated with placebo). In part 3 of the study subjects received dabigatran similar to that in part 2 followed by PBO or idarucizumab, 5g plus 2.5 g intravenously each over 5 minutes administered 15 minutes apart. Twelve subjects were treated (9 subjects treated with idarucizumab and 3 subjects treated with placebo). No concomitant therapy was allowed in this trial. The objective of the study was to investigate the safety, tolerability, and pharmacokinetics of intravenous doses of idarucizumab and to explore the effect of different doses of idarucizumab administered at or close to the steady state of dabigatran. The primary endpoint of this trial was the incidence of drug-related adverse events in each study part. Secondary endpoints were comprised of evaluation of pharmacokinetic parameters and pharmacodynamic parameters to demonstrate the reversal of the dabigatran anticoagulant effect by idarucizumab. Pharmacodynamic parameters secondary endpoints included activated partial thromboplastin time (aPTT), dilute thromboplastin time (dTT), thrombin time (TT) and ecarin clotting time (ECT) from baseline to day 3 and 4 after the last dose of idarucizumab. Descriptive statistics for safety, pharmacokinetic and pharmacodynamic endpoints were used to describe the results of the study. The sponsor's tables below show the study schedule. AEs were coded

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and graded according to MedDRA 17.0 criteria. The study was conducted under Good Clinical Practices and Declaration of Helsinki Guidelines. A signed Written Informed Consent Form was required in order to enroll in the study. An Institutional Review Board (IRB) and Data Safety Monitoring Board (DSMB) reviewed and monitored the study.

Table 2. Study Schedule 1321.1

Part 1: Single Dose groups 1 to 10 (1 hour infusion)

Trial period	Scr.		Treatment period																								E.o.s.
Visit	1		2																								3
Day	-21 to -1	-1	1																				2	3	4		6 to 14
Planned Time Related to end of infusion [h:min]			Before	-1:00	-0:30	0:00	0:02	0:05	0:10	0:15	0:30	0:45	1:00	1:30	2:00	2:30	3:00	4:00	6:00	8:00	10:00	12:00	16:00	24:00	48:00	72:00	
Relative daytime [h:min]			7:45	8:00	8:30	9:00	9:02	9:05	9:10	9:15	9:30	9:45	10:00	10:30	11:00	11:30	12:00	13:00	15:00	17:00	19:00	21:00	1:00	9:00	9:00	9:00	
Administration of BI 655075			|—X—|																								
Physical examination	X²	X																X						X	X	X⁶	X²
Vital signs	X¹⁶	X¹⁶			X¹⁶	X¹⁶				X	X¹⁶		X	X	X¹⁶		X	X¹⁶	X	X		X¹⁶		X¹⁶	X	X	X
ADA/ Cytokines¹⁴		X																X¹⁴						X¹⁴			X¹³
Continuous ECG and pO2 monitoring				——————————————X——————————————																							
12-lead ECG	X	X	X		X	X					X		X	X	X		X	X	X	X		X		X	X	X	X
Laboratory	X⁷	X																X						X		X	X
Urinalysis	X¹⁵	X¹⁵													X¹⁵			X¹⁵				X¹⁵		X¹⁵	X¹⁵	X¹⁵	
Blood sampling for PK¹²		X¹			X	X	X	X	X	X¹	X	X	X	X	X		X	X	X	X		X	X	X	X	X	X
Urine collection for PK*⁸		X		—————————————————X—————————————————															—X—			—X—	—X—	—X—	
In-house			<————————————————————————X————————————————————————>																							
Adverse events / Concomitant medication			<————————————————————————X————————————————————————>																								>

*Urine sampling for PK relative to the End of infusion (group 4-10): pre-dose, -1– 6 h, 6 – 12 h, 12 – 24 h, 24 – 48 h, 48 – 72 h

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Part 1: Single Dose groups 11 to 13 (short infusion)

Trial period	Scr.	Treatment period																								E.o.s.
Visit	1	2																							3
Day	-21 to -1	-1	1																			2	3	4	6 to 14
Planned Time Related to end of infusion [h:min]			Before[3]	-0:05	0:00	0:02	0:05	0:10	0:15	0:30	0:45	1:00	1:30	2:00	2:30	3:00	4:00	6:00	8:00	10:00	12:00	16:00	24:00	48:00	72:00	
Relative daytime 5 min.infusion[h:min]			7:45	8:00	8:05	8:07	8:10	8:15	8:20	8:35	8:50	9:05	9:35	10:05	10:35	11:05	12:05	14:05	16:05	18:05	20:05	24:05	8:05	8:05	8:05	
Randomisation		X																								
Administration of BI 655075			⊢X⊣																							
Physical examination[2]	X[2]	X															X						X	X	X[6]	X[7]
Vital signs	X[16]		X[16]		X				X	X[16]	X	X		X[16]		X	X[16]	X	X		X[16]		X[16]	X	X	X
ADA/ Cytokines[14]		X															X[14]						X[14]			X[13]
Continuous ECG and pO2 monitoring			⊢---------------------------X--------------------------⊣																							
12-lead ECG	X	X		X					X	X		X	X	X		X	X	X	X		X		X	X	X	X
Laboratory	X[7]	X															X						X		X	X
Urinalysis	X[15]	X[15]									X[15]						X[15]				X[15]		X[15]	X[15]	X[15]	
Blood sampling for PK[12]		X[1]		X	X	X	X	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine collection for PK*		X	⊢------------------------X-----------------------⊣⊢--X--⊣⊢--X--⊣⊢-X-⊣⊢X⊣⊢X⊣																						
In-house		←---X--→																								
Adverse events / Concomitant medication		←---X--→																								

*Urine sampling for PK relative to the End of infusion: pre-dose, -5 min – 4 h, 4 – 8 h, 8 – 12 h, 12 – 24 h, 24 – 48 h, 48 – 72 h

Part 2: Single Dose groups 14 to 16 (short infusion administered in steady state of dabigatran) General overview

Trial period	Scr.	Treatment period								e.o.s.
Visit	1	2								3
Day	-21	-1	1	2	3	4	5	6	7	9 to 18
Informed consent	X									
Dabigatran Administration			X	X	X	X				
In-/Exclusion Criteria	X	X								
Administration of BI 655075						X				
Physical examination	X[2]	X				X	X			X[2]
Drug +Virus Screening[4]	X	X[1]								
Vital signs	X[16]	X	X	X	X	X[16]	X	X	X	X
12-lead ECG	X	X	X	X	X	X	X	X	X	X
Continuous ECG,, sPO2 monitoring						X				
Safety Laboratory (blood, urine)	X[7], X[15]	X				X	X[15]	X[15]	X	X
ADA/Cytokines[14]			X[5]			X[14]	X[14]			X[13]
Adverse events	←----------------------------------X------------------------------→									
In-house		X	X	X	X	X	X	X		
Local tolerability								X		
Discharge							X			
Urine collection for PK/PD			X		X	X	X	X	X	
Blood sampling for dabigatran PK/PD[12]		X	X		X	X	X	X	X	
ACT and additional PD parameters[11]		X	X		X	X	X	X	X	
Blood sampling for PK of BI 655075			X			X	X	X	X	

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Part 2: Single Dose groups 14 to 16 (short infusion administered in steady state of dabigatran)

Visit	Day	Planned Time[9] [h:min]	time (actual day) [h:min]	Laboratory / Urinalysis	Physical examination	Dabigatran administration	Administration of BI 655075	PK$_{blood}$ of BI 655075[12]	ACT and additional Pb parameters	PK/PD$_{blood}$ dabigatran[10]	PK$_{urine}$ ***	12-lead ECG	vital signs	ECG and pO2 -monitoring	ADA/ Cytokines[14]	Adverse events/Con. med
	-1	24:00		X	X				X		X					
	1	0:00	7:00			X		X[5]	X[5,17]	X[5]	X[5]	X[5]	X[5]			
	1	12:00	19:00			X										
	2	24:00	7:00			X							X[5]			
	2	36:00	19:00			X										
2	3	48:00	7:00	X	X				X[3]	X[5]		X[5]	X[5]			
2	3	49:00	8:00							X						
2	3	50:00	9:00							X						
2	3	50:30	9:30						X[11]	X						
2	3	51:00	10:00							X						
2	3	52:00	11:00							X						
2	3	54:00	13:00						X[11]	X						
2	3	56:00	15:00							X						
2	3	58:00	17:00							X						
2	3	60:00	19:00			X			X[3]	X[5]						
2	4	72:00	7:00	X	X	X			X[3]	X[5]						
2	4	73:00	8:00							X						
2	4	73:55	8:55				▲X▼	X[5]	X[3]	X[5]		X[5]	X[5,16]		X[5]	
2	4	74:00	9:00					X		X		X	X	▲		
2	4	74:02	9:02					X								
2	4	74:05	9:05					X						X		
2	4	74:10	9:10					X		X						
2	4	74:15	9:15					X				X	X	▼		

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Part 2: Single Dose groups 14 to 16 (short infusion administered in steady state of dabigatran)

Visit	Day	Planned Time [h:min] [18]	time (actual day) [h:min]	Laboratory/ Urinalysis	Physical examination	PK samples of BI 655075 [12]	ACT and additional PD parameters [11]	PK/PD shed dabigatran [10]	PK urine ***	12-lead ECG	vital signs BP, PR	ECG and pO2 monitoring [14]	ADA/Cytokines [14]	Adverse events/Con. med
2	4	74:30	9:30			X	X[17]	X		X	X[16]			
		74:45	9:45			X				X	X			
		75:00	10:00	X[15]		X	X	X		X	X	X		
		75:30	10:30			X				X	X			
		76:00	11:00			X	X	X		X	X[16]			
		76:30	11:30			X								
		77:00	12:00			X				X	X		X[14]	
		78:00	13:00	X	X	X	X[17]	X		X	X[16]			
		80:00	15:00			X	X	X		X	X			
		82:00	17:00			X	X	X		X	X			
		84:00	19:00			X	X	X						
		86:00	21:00	X[15]		X		X		X	X[16]			
		90:00	01:00			X		X						
	5	98:00	9:00	X	X	X	X[17]	X		X	X		X[14]	
	6	122:00	9:00	X[15]		X	X	X		X	X			
	7	146:00	9:00	X		X	X	X		X	X			
3	EOS 9 to 18[2]			X[7]	X					X	X		X[13]	

*Urine sampling on Day 3 relative to dabigatran dose: 3 – 2 h, 2 – 6 h, 6 – 10 h, 10 – 12 h;

**Urine sampling on Day 4 relative to the end of BI 655075infusion: -2h – -5 min, -5 min – 4 h, 4 – 8 h, 8 – 10, 10 - 12 h, 12 – 24 h, 24 – 48 h, 48 – 72 h

1. In dose groups 10 and 13, additional PD samples are obtained for dTT, ECT aPTT, ACT, TT and ETP at time points before and 15 min after end of BI 655075 infusion.
2. Including physical examination, review of vital signs, ECG, and laboratory; additionally at the screening including subject information, informed consent, demographics, relevant medical history, concomitant medication, drug and virus screening, review of inclusion and exclusion criteria
3. Within 2 hours prior to the planned dosing, planned time -2:00 will be used.
4. Virus – on screen only;
5. Predose.
6. Local tolerability inclusive.
7. Protein electrophoresis only at screen
8. Urine collection starts from dose group 4 onwards, no urine collection for dose groups 1-3
9. On day 3 – relative to the dabigatran administration, on day 4 – relative to the end of infusion
10. PD includes for each sampling point: hemoclot (dTT), aPTT, ECT, TT
11. Additional PD parameters for: shed blood, washed blood and endogenous thrombin potential (ETP) where indicated
12. PK and PD sampling times may be adapted based on information obtained during trial conduct
13. ADAs samples will be taken at baseline, EOS, 4 weeks and 3 months after BI 655075 administration
14. IL1, IL6, TNF and Interferon Gamma will be collected baseline, 4h and 24h postdose. These samples only to be analyzed in case of specific adverse events suggestive for cytokine release
15. Urinalysis including α1 microglobulin, albumin and IgG
16. Body temperature inclusive
17. Additional PD parameters (shed blood, washed blood and ETP) inclusive
18. Assumed dosing time is 8:00am, but the actual dosing time may differ for a particular subject

Sponsor's table Study 1321.1 Protocol pages 6-11

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Clinical Review
Andrew Dmytrijuk, M.D.
BLA 761025
Praxbind (Idarucizumab)

In study 1321.1 all subjects completed the study. The mean age was 33.0 years, ranging from 19 to 46 years, and the mean BMI was 24.16 kg/m^2, ranging from 19.2 to 29.7 kg/m^2. In this study 97% of subjects were white. Demographic characteristics were similar for the different treatment groups.

Mean plasma concentration of idarucizumab versus time profiles that were obtained from part 1 of study 1321.1 show that single doses of placebo or idarucizumab maximum plasma concentration of idarucizumab (Cmax) was achieved around the end of the idarucizumab infusion, followed by a rapid mono- to biphasic decline in plasma concentrations as shown in the sponsor's figure below. A terminal phase was observed for doses of 600 mg or higher. Idarucizumab was detectable in plasma up to 16 h after infusion of 1 g and up to 24 h following infusion of higher doses.

Figure 1. Mean Plasma Concentration of Idarucizumab vs Time Profiles Part 1
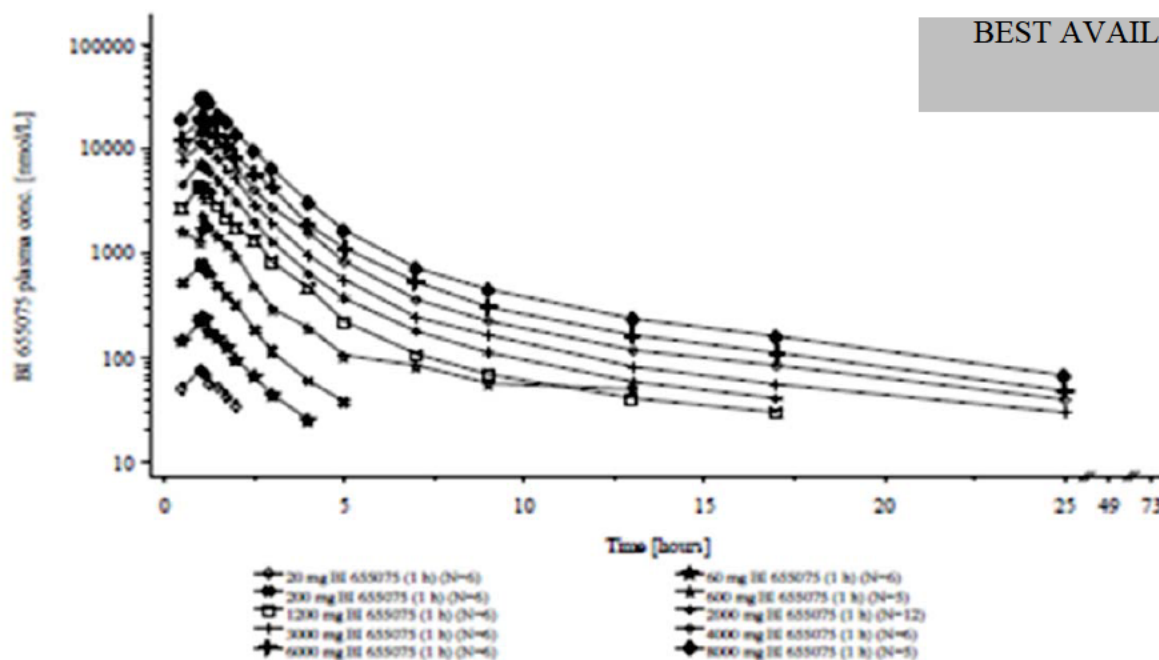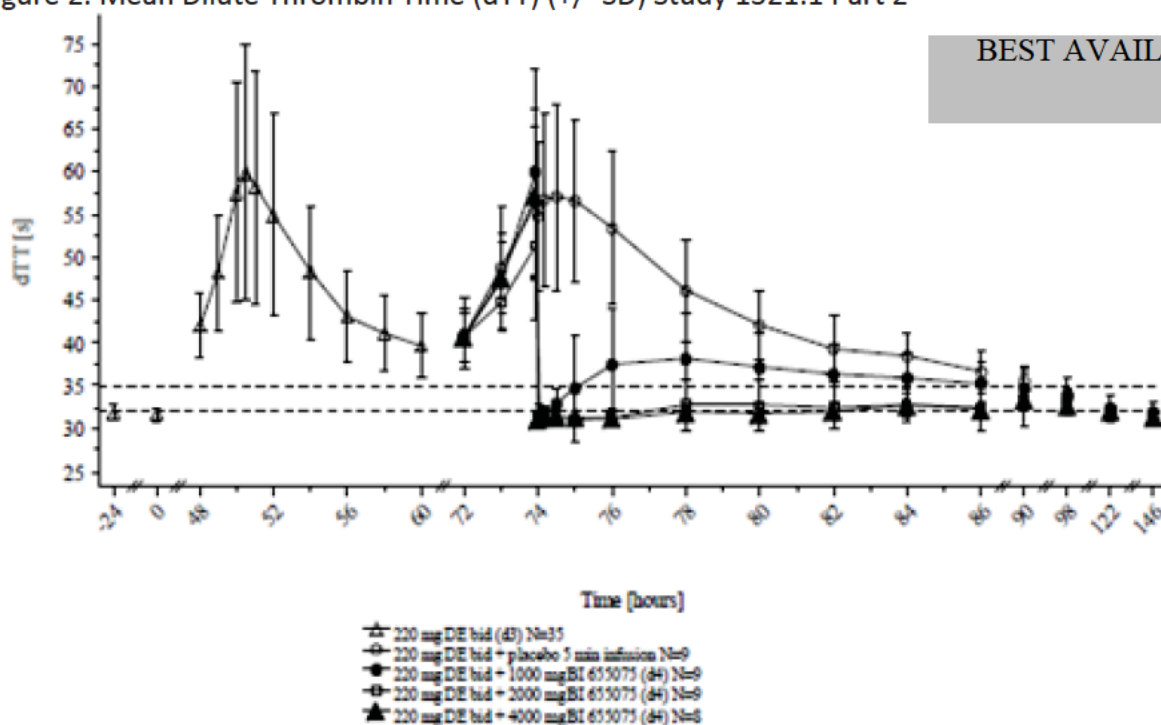

Sponsor's Figure 11.5.2.1.1:1 from Study Report 1321.1 page 106

The sponsor's figure below summarizes the result of the reversal of anticoagulation effect of dabigatran by idarucizumab from part 2 of the study for the dTT test over time. Similar results were observed for the other pharmacodynamic coagulation tests. Blood coagulation times were determined by central laboratory analysis of aPTT, dTT, ECT and TT. ACT was measured at bedside. The upper limit of normal (ULN) reference values were determined based on the mean values + 2 SD of individual baseline measurements (N=110 subjects) in study 1321.1. The dashed lines represent the ULN. Reversal of dabigatran-mediated anticoagulation is defined as "immediate" if the effect of dabigatran was reversed at the end of idarucizumab infusion.

"Complete reversal" is defined as the return of the mean coagulation time to below the ULN. "Sustained reversal" is defined by the mean coagulation time remaining below the ULN during the entire observation period, i.e., 72 hours (hour 74-146). The sponsor's figure below shows the time course of the mean dTT during part 2 of the study. Dabigatran 220mg was administered orally for 3 days followed by a forth dose on day 4. When administered alone dabigatran has the expected anticoagulation effect on the dTT, aPTT, ECT, TT and ACT (shown in the figure as the first and second dTT peaks). Subsequent administration of placebo did not result in a rapid reversal of the dabigatran effect (see open circles). However, administration of idarucizumab after dabigatran appeared to reverse the anticoagulant pharmacodynamic effect of dabigatran (shown as near immediate decrease of pharmacodynamic marker near hour 74). Administration of 1g of idarucizumab resulted in immediate and complete reversal with subsequent partial return of the dabigatran anticoagulant effect starting between 30 min to 2 hours after the end of the infusion (see filled circle). Administration of 2g of idarucizumab resulted in immediate, complete, and sustained reversal with the clotting assays diluted thrombin time (dTT) and activated partial thromboplastin time (aPTT), while the mean ecarin clotting time (ECT) values between 6 and 16 hours after the end of the infusion were slightly above the upper limit of normal (ULN) (see open square). Administration of 4g of idarucizumab resulted in immediate, complete, and sustained reversal with dTT, ECT and aPTT (see filled triangle).

Figure 2. Mean Dilute Thrombin Time (dTT) (+/- SD) Study 1321.1 Part 2

Sponsor's Figure 11.5.3.3:3 from Study Report 1321.1 page 142

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Andrew Dmytrijuk, M.D.
BLA 761025
Praxbind (Idarucizumab)

The table below summarizes the mean pharmacodynamic effect of idarucizumab over time for the 12 subjects treated in part 3 (9 subjects treated with idarucizumab and 3 treated with PBO). Subjects received dabigatran 220mg orally twice daily for 3 days and an additional single 220mg dose of dabigatran on day 4 about 2 hours before the first dose of idarucizumab. Idarucizumab was then administered at 5g intravenously over 5 minutes followed 15 minutes later by 2.5 g intravenously over 5 minutes. The clotting assays that were tested include dTT, aPTT, ECT, TT and ACT. The upper table shows the results of the idarucizumab treatment group and the lower table shows the results of the PBO treatment group. Highlighted are the Pre-idarucizumab or Pre-PBO time point which was measured just prior to idarucizumab or PBO administration and the 30 minute time points after the last idarucizumab or PBO infusion. Selected time points that are also shown are the 24 hour and 72 hour time points after the last administration of idarucizumab. In the upper table a relative comparison of the clotting tests before and after the administration of idarucizumab shows that there is a reversal of the anticoagulant effect of dabigatran as shown by the decrease in assay clotting times by idarucizumab which is not evident in the lower table for those treated with PBO. At 24 and 72 hours the clotting test results are similar to those at the 30minute time point for idarucizumab and for PBO as well. Therefore, the clotting tests were reversed within 30 minutes of the completion of study drug administration. Similar results to these were observed for subjects in part 2 of the study where subjects were treated with dabigatran followed by single doses idarucizumab or PBO.

Table 3. Part 3 Mean Pharmacodynamic Effect Over Time

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Reference ID: 3812170

Clotting Assay, Seconds (Standard Deviation)	Pre-Idarucizumab	30 Minutes After Idarucizumab	24 Hours After Idarucizumab	72 Hours After Idarucizumab
dTT	48.7 (7.3)	31.4 (1.8)	32.2 (1.9)	33.2 (1.9)
aPTT	65.0 (9.2)	35.3 (2.0)	34.6 (2.4)	33.9 (1.2)
ECT	92.7 (19.6)	35.7 (1.6)	35.7 (1.8)	36.9 (1.4)
TT	112.0 (19.3)	12.5 (0.8)	12.3 (0.6)	13.1 (0.5)
ACT	182.0 (14.0)	115 (10.2)	127 (13.4)	130 (8.0)

Clotting Assay, Seconds (Standard Deviation)	Pre-Placebo	30 Minutes After Placebo	24 Hours After Idarucizumab	72 Hours After Idarucizumab
dTT	47.3 (16.2)	47.6 (17.5)	34.1 (4.2)	32.1 (3.3)
aPTT	56.9 (7.9)	62.1 (9.9)	39.7 (0.0)	33.1 (0.1)
ECT	88.9 (35.5)	86.4 (33.4)	41.6 (0.1)	37.0 (1.1)
TT	101.0 (47.9)	103 (54.2)	26.9 (11.2)	13.5 (0.1)
ACT	179.0 (28.3)	157 (17.7)	139 (7.1)	132 (3.54)

Reviewer tables derived from Sponsor's Tables 77-90 Study Report 1321.1 pages 4688-4710

Idarucizumab appeared to be generally well tolerated. The most frequently reported AEs in ≥ 3 subjects in part 1 were headache (n= 9 idarucizumab, 2 PBO), nasopharyngitis (n= 4 idarucizumab, 1 PBO), back pain (n= 4 idarucizumab, 1 PBO) and skin irritation (n= 3 idarucizumab, 2 PBO). In parts 2 and 3 of the study there were no adverse events which were experienced by at least 5 subjects. There were 3 subjects treated with idarucizumab and 0 subjects treated with PBO who reported dizziness/presyncope in parts 2 and 3. Adverse events were all classified as mild and resolved without sequelae. For a short period of up to 4 hours immediately following the infusion with idarucizumab, proteinuria with small molecular weight proteins was noted, which was believed to be due to the excretion of idarucizumab in the urine in a small number of patients. There was no evidence of the development of anti-drug neutralizing antibodies among the 157 treated subjects.

Study 1321.2

Study 1321.2 titled "Randomized, Double-Blind, Placebo-Controlled, Two-Way Crossover

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Reference ID: 3812170

Phase Ib Study To Investigate The Safety, Tolerability, Pharmacokinetics And Pharmacodynamics Of BI 655075 (Idarucizumab) And To Establish The Efficacy Of BI 655075 In Reversal Of Dabigatran Anticoagulant Activity In Volunteers" is a safety, tolerability, pharmacokinetic and pharmacodynamic study.   The study was a pharmacokinetic and pharmacodynamic, 2-way crossover, single dose study with 7 groups. The overall duration of the trial was approximately 90 days with 2 periods. There were 46 subjects enrolled in this study (12 subjects with renal impairment defined as mild renal impairment CrCl ≥ 60 to <90 mL/min and moderate renal impairment was defined as CrCl <60mL/min - ≥30mL/min. The primary endpoint is the pharmacodynamic reversal of dabigatran as measured by clotting assays, dTT, TT, ECT, aPTT, ACT. In this study idarucizumab 1 to 5 g, with and without dabigatran 220mg (150mg in mild to moderately renally impaired patients) was administered orally twice daily.   The primary analysis investigated whether at least 1 assay value (of the 2 sampling times at the end of the infusion and 10 min later) of the coagulation parameters dTT and ECT was reversed after dabigatran treatment. Generally, a similar study schedule was used in study 1321.1 compared to study 1321.2. AEs were coded and graded according to MedDRA 17.0 criteria. Descriptive statistics were used to analyze the study results. The study was conducted under Good Clinical Practice and Declaration of Helsinki Guidelines. A signed written informed consent was required in order to enroll in the study. All subjects completed the study.

The overall mean age was 63.8 years (standard deviation 9.2 years) and 44/46 (96%) subjects were white. Twelve subjects (6 each) were enrolled with mild renal impairment or moderate renal impairment. The sponsor's table below shows the demographics of the subjects treated in study 1321.2.

Table 4. Demographics Study 1321.2

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Reference ID: 3812170

	High dose/ healthy (45-64 y)	High dose/ elderly (65-80 y)	High dose/ mild renal impairment	High dose/ moderate renal impairment	Medium dose/ healthy (45-64 y)	Low dose/ elderly (65-80 y)	Low dose/ mild renal impairment	Total
Treated subjects, N (%)	6 (100)	8 (100)	6 (100)	6 (100)	6 (100)	8 (100)	6 (100)	46 (100)
Sex, N (%)								
Male	3 (50.0)	6 (75.0)	4 (66.7)	3 (50.0)	3 (50.0)	4 (50.0)	4 (66.7)	27 (58.7)
Female	3 (50.0)	2 (25.0)	2 (33.3)	3 (50.0)	3 (50.0)	4 (50.0)	2 (33.3)	19 (41.3)
Age, mean (SD) [years]	50.0 (4.6)	67.5 (1.6)	68.7 (4.5)	72.0 (2.6)	53.2 (6.3)	70.0 (2.8)	62.0 (9.9)	63.8 (9.2)
Race, N (%)								
White	6 (100)	8 (100)	5 (83.3)	6 (100)	6 (100)	7 (87.5)	6 (100)	44 (95.7)
American Indian/ Alaska Native	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	1 (12.5)	0	1 (2.2)
Black/African American	0	0	1 (16.7)	0	0	0	0	1 (2.2)
Weight, mean (SD) [kg]	76.0 (20.2)	80.8 (7.0)	71.7 (7.6)	65.5 (12.2)	78.2 (10.0)	73.8 (8.9)	71.7 (6.8)	74.2 (11.2)
BMI, mean (SD) [kg/m²]	24.35 (3.12)	27.48 (3.27)	26.43 (1.93)	22.83 (1.92)	26.40 (2.91)	26.73 (2.33)	25.38 (1.58)	25.78 (2.80)

Source data: Table 15.1.4: 1

Sponsor's table Study Report 1321.2 page 98

In this study after treatment with idarucizumab, all subjects 46/46 (100%) showed reversal of the dabigatran-induced prolongation of clotting time regardless of the degree of renal impairment or age. When receiving placebo, none of the subjects 0/46 (0%) showed reversal as shown in the sponsor's table below.

Table 5. Reversal of Dabigatran Induced Clotting Time Study 1321.2

Treatment group	dTT		ECT	
	Placebo N (%)	Idarucizumab N (%)	Placebo N (%)	Idarucizumab N (%)
By dose				
1 g, N=14	0	14 (100)	0	14 (100)
2.5 g, N=6	0	6 (100)	0	6 (100)
5 g, N=26	0	26 (100)	0	26 (100)
By subject group				
Healthy subjects (45 to 64 years), N=12	0	12 (100)	0	12 (100)
Elderly subjects (65 to 80 years), N=16	0	16 (100)	0	16 (100)
Subjects with mild renal impairment 45 to 80 years), N=12	0	12 (100)	0	12 (100)
Subjects with moderate renal impairment (45 to 80 years), N=6	0	6 (100)	0	6 (100)

[1] Defined as reversal to Baseline 1 based on individual measurement values within a group

Sponsor's table Study Report 1321.2 page 131

Idarucizumab was generally well tolerated in study 1321.2. Adverse events in this study were characterized as mild or moderate. Adverse events that occurred in ≥ 4 subjects in this study was headache (n=4 idarucizumab and 1 PBO). The sponsor reported that a total of 5 subjects had no evidence of anti-drug antibodies prior to idarucizumab but subsequently had positive anti-drug antibody titers at 4 weeks (n= 2 subjects) or at the 3 month follow-up (n=5 subjects).

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These anti-idarucizumab antibodies were directed against the C-terminus and were considered to be non-blocking antibodies.

Study 1321.5

Study 1321.5 is a supportive study in 80 healthy Japanese male subjects which evaluated the pharmacokinetics of a single dose of idarucizumab compared to placebo. Similar pharmacodynamic results were observed in this subject population compared to study 1321.1. No serious adverse events were reported in this study. Overall the adverse event profile was similar to that reported in studies 1321.1 and 1321.2.

Study 1321.3

Study 1321.3 is titled, "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, the REVERSE –AD trial". This study is an open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to 300 adult patients. The primary objective is to demonstrate reversal of the anticoagulant effect of dabigatran in patients treated with dabigatran who have uncontrolled or life-threatening bleeding requiring urgent intervention, and in patients treated with dabigatran who require emergency surgery or other invasive procedure. The key enrollment criteria are bleeding that requires a reversal agent in the opinion of the physician, urgent requirement for surgery or an invasive procedure where adequate hemostasis is required and patients must be taking dabigatran. In this study Idarucizumab is administered at a 5g fixed dose administered as two 2.5g doses administered over 5-10minutes separated by 15 minutes or as a bolus. Biomarker endpoints are the basis for determination of efficacy in this trial. Ecarin clotting time (ECT), diluted Thrombin Time (dTT), activated Partial Thromboplastin Time (aPTT) and Thrombin Time (TT) are measured in a central laboratory. The sponsor's table below shows the study schedule. The study is being conducted under Declaration of Helsinki and Good Clinical Practices Guidelines. A signed Written Informed Consent is required to enroll into the study. An IRB and DSMB have reviewed and are monitoring the study.

Table 6. Study Schedule 1321.3

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Investigations/Tests and Procedures	Screening Period	Treatment Period		Safety Follow-Up Period			
Visit Number	1	2.1	2.2	3	4	5	6 (End of study)
Visit Description	Patient screening	Vial 1	Vial 2	24-hours after vial 2	7 days after vial 2	30 days after vial 2	90 days after vial 2
Visit Day(s)	1	1	1 (no later than 15 min after vial 1)	2 (± 2 hours)	7 (+ 3 days)	30 (± 7 days)	90 (± 7 days)
Informed consent[1]	X						
Inclusion / exclusion criteria	X						
Confirm dabigatran use	X						
Medical History	X						
Demographics	X						
Physical Exam and Vital Signs	X	X[7]	X[7]	X[7]	X[7]	X2	X
Bleed assessment	X	X	X	X	X	X	X
Surgery/Procedure assessment	X	X	X	X	X	X	X
Study Drug Administration		X	X				
PK/PD Blood Draw[3]	X	X	X	X		X	X
Local Safety Blood Draw[4,9]	X[8]	X[8]	X[8]	X			

Investigations/Tests and Procedures	Screening Period	Treatment Period		Safety Follow-Up Period			
Visit Number	1	2.1	2.2	3	4	5	6 (End of study)
Visit Description	Patient screening	Vial 1	Vial 2	24-hours after vial 2	7 days after vial 2	30 days after vial 2	90 days after vial 2
Pregnancy Testing[5]	X					X	
Blood draw for genomic testing						X10	
Study drug accountability			X				
ECG	X				X		
Adverse Events	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X
Re-start anticoagulant therapy				X			
Conclusion of patient participation[6]							X

1-Written informed consent.
2-Blood pressure, pulse rate only.
3-Blood sampling for central PD (biomarker) and pharmacokinetic measurements will occur:
Prior to administration of the first vial, just prior to the second vial, as well as between 10 and 30 min, 1, 2, 4, 12,24 hours, and 30, and 90 days after the end of the infusion of the second vial. For details refer to table 5.5.2.1: 1. Time will be recorded for every blood sample taken. Actual time for the start and end of the infusion will be recorded.
4-Includes Hematology and Chemistry.
5-Local urine pregnancy test in women of childbearing potential. A negative test must be obtained prior to study drug administration.
6-Conclusion of patient participation also needs to be completed if the patient withdraws prematurely following first vial of study medication.
7-Blood pressure and heart rate hourly while the patient is in the emergency department, then every 4 hours for the next 72 hours or until discharge.
8-Draw blood for local lab aPTT at baseline, just prior to the second vial, 10 to 30 minutes, and 12 hour after second vial.
9-Additional local lab testing may be done at the discretion of the treating physician to facilitate patient clinical management.
10-Pharmacogenomic sample can be taken at visit 5 or visit 6.

Sponsor's table Study Report 1321.3 page 577

Efficacy is based on central laboratory determination of reversal of the anticoagulant effect of

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dabigatran, using several coagulation tests, i.e., ECT, dTT, TT. No dosing or patient management decisions are based on central lab determination of reversal. The interim report contains data from 123 adult patients enrolled from June 2014 until April 1, 2015. The study is ongoing.   An interim report of the results from study 1321.3 was submitted by the sponsor in BLA 761025 supporting document 13 letter date June 19, 2015 and the results of this interim report are considered supportive of the safety and efficacy of idarucizumab.

All of the 123 patients in this analysis received the pre-specified 5 g dose of idarucizumab. The sponsor states that the infusion time was (b)(4) minutes. There were 66 patients in Group A (bleeding) and 57 patients in Group B (surgery). The demographics of patients enrolled in study 1321.3 are shown in the sponsor's table below. Overall, the baseline demographics were similar between groups. Overall, the median age was 77 years (range 48-93), 65/123 (53%) were male and 105/123 (85%) were white. There were 49/123 (40%) of patients enrolled with moderate to severe renal insufficiency, i.e., CrCl (Cockroft-Gault) < 50mL/min.   Overall, the median time from last dabigatran exposure to the time of idarucizumab administration was 16 hours (range 1-94 hours). Nearly all patients, i.e., 117/123 (95%) were treated with dabigatran for the atrial fibrillation indication. Most patients, i.e., 80/123 (65%) were treated with dabigatran 110mg orally twice daily. In group A (serious bleeding group) there were 27/66(41%) who presented with gastrointestinal bleeding, 24/66 (36%) patients presented with intracranial bleeding, the remaining 15/66 (22%) of patients had serious bleeding in other areas such as trauma, intramuscular, retroperitoneal, intra-pericardial, intra ocular and one bleeding location was not yet identified by the sponsor.   Of the 57 patients in group B (urgent surgery group) surgery that was required in ≥ 3 patients was bone fractures 13/57 (23%) of patients, gall bladder disease (cholecystitis, cholelithiasis) 7/57 (12%) of patients, joint/wound infection 4/57 (7%) of patients and acute appendicitis, small bowel obstruction, bowel perforation in 3/57 (5%) each, respectively.

Table 7. Demographics Study 1321.3

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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)

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Characteristic	Group A	Group B	Total
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.
Sponsor's table 4 Month Safety Update Report Study 1321.3

Three patients did not undergo planned surgery.

- Patient number   (b) (6)   from   (b) (6)   had taken an overdose of dabigatran (estimated to approximately 125 capsules, total dose unknown) and was referred to a hospital participating in the study for hemodialysis of dabigatran. However, during the preparation for dialysis, the patient was treated with idarucizumab and the clotting tests normalized, no bleeding occurred and the dialysis was cancelled.
- Patient number   (b) (6)   from the same site in   (b) (6)   presented with acute mesenteric ischemia, was treated with idarucizumab but was too unstable to undergo the planned exploratory laparoscopy. The patient died 1 day later due to circulatory shock.
- Patient number   (b) (6)   from the   (b) (6)   was scheduled to undergo a gastric perforation repair and was treated with idarucizumab. However, the patient was too unstable to undergo the planned surgery. She died 1 day later of peritonitis and acute post-hemorrhagic anemia.

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Clinical Review
Andrew Dmytrijuk, M.D.
BLA 761025
Praxbind (Idarucizumab)

Reviewer comment section 6. Studies 1321.1 and 1321.2 appear to be reasonably well designed, from a clinical perspective, to demonstrate that 5g of idarucizumab in normal healthy volunteers, elderly patients or patients with mild/moderate renal insufficiency can reverse the pharmacodynamic effect of dabigatran as demonstrated by decrease in assay clotting times by idarucizumab which is not evident in those subjects treated with PBO. The proportion of change in tests may not be similar because the coagulation tests evaluate different points along the clotting cascade and have different sensitivities and specificities in terms of demonstrating the dabigatran pharmacodynamic effects. The dTT and ECT assays are sensitive tests to evaluate the pharmacodynamic effects of dabigatran. (Van Ryn, 2010) Idarucizumab appeared to be generally well tolerated in this subject population with only mild/moderate AEs reported primarily reported to be headache, nasopharyngitis, back pain and skin irritation in ≥ 4 subjects. The clinical significance of the immunogenicity results observed in study 1321.2 is not clear. Although 5 subjects in this study had no evidence of anti-drug antibodies prior to idarucizumab treatment and subsequently had positive anti-drug antibody titers at 4 weeks (n= 2 subjects) and at the 3 month follow-up (n=5 subjects), these antibodies were directed against the C-terminus and were considered to be non-blocking antibodies. The results of study 1321.3 are discussed in detail in section 7 Review of Effectiveness and section 8 Review of Safety. Patients were enrolled in study 1321.3 on the basis of their history of dabigatran intake and the assumption that the drug may have been contributing to bleeding or could increase the risk of surgery. These are scenarios that are likely to mirror clinical practice. The strengths of these studies, i.e., 1321.1, 1321.2 and 1321.3 include the broad inclusion criteria (study 1321.3) and confirmation of the results of the coagulation tests reflected dabigatran reversal by determination of the concentrations of unbound drug. The major limitation of study 1321.3 is the lack of a control group. A cohort design for study 1321.3 is reasonable because it seems unethical to randomly assign patients to receive placebo or no active treatment. Although other therapies such as PCC may be used in an attempt to reverse the pharmacodynamic effect of dabigatran these therapies have their effects at points in the clotting cascade prior to thrombin. Other, management approaches that could be considered include supportive care with blood products such as fresh frozen plasma, fresh or packed red blood cell (RBCs) transfusions or packed platelet transfusions. However, with these agents thrombin is a critical factor for coagulation. Dabigatran can be hemodialyzed out of a patient's circulation. However, this approach may not be optimal in a situation that requires rapid anticoagulant reversal.

# 7   Review of Effectiveness

7.1.   Assessment of Efficacy Study 1321.3

The design of study 1321.3 was discussed in detail in section 6 Review of Relevant Individual Trials Used to Support Efficacy.

7.1.1. **Primary Endpoints**

The sponsor's figure below shows the reversal of the dabigatran pharmacodynamic effect by idarucizumab. The maximum reversal of ECT or dTT in the first 4 hours was the primary endpoint. The dTT was tested in 40 patients in group A (serious bleeding) and 28 patients in group B (urgent surgery) at four hours. The ECT was tested in 47 patients in group A and 34 patients in group B. A maximal reversal (100%) of dTT was achieved in 39/40 (98%) of patients in group A and 26/28 (93%) of patients in group B. A maximal reversal (100%) of ECT was achieved in 42/47 (89%) of patients in group A and 30/34 (88%) of patients in group B. The sponsor's figure below shows that dTT and ECT decrease to normal levels within 10-30 minutes of idarucizumab administration and are sustained for a period of 24 hours after the last dose of idarucizumab administration.

Figure 3. Reversal of the Pharmacodynamic Effect of Dabigatran by Idarucizumab Study 1321.3
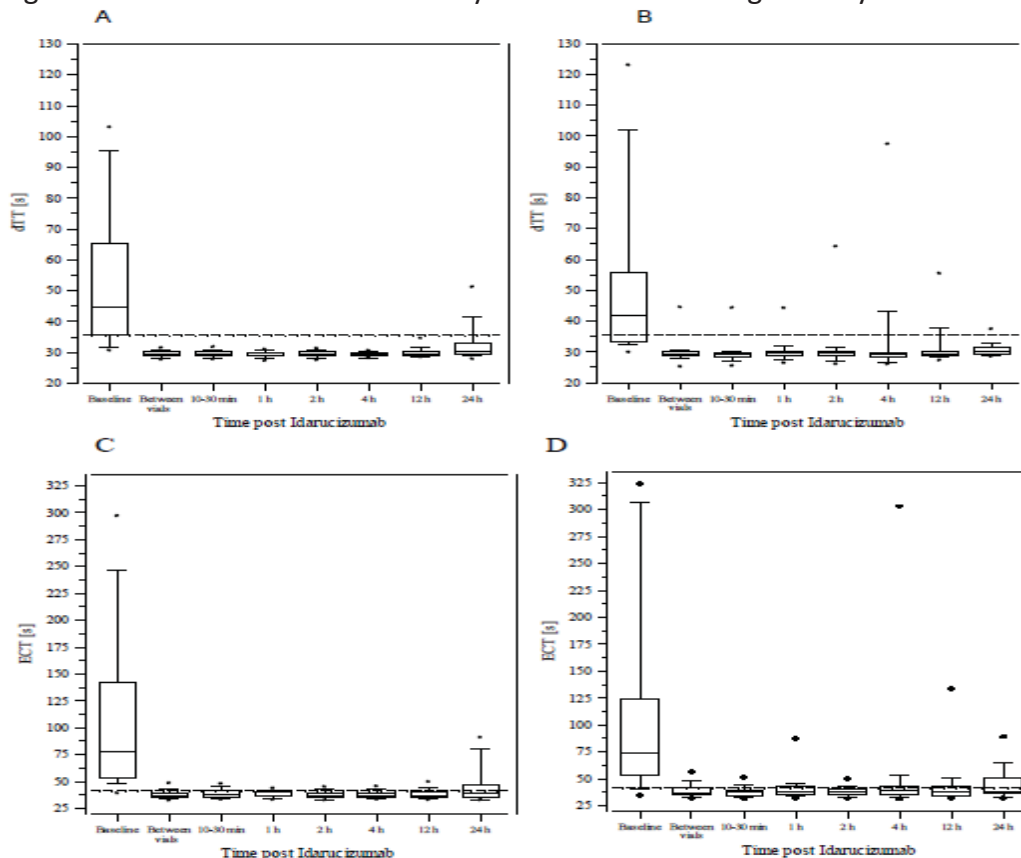

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Dilute thrombin times (top) and ecarin clotting times (bottom) with Group A on the left and Group B on the right, in anticoagulated patients in Study 1321.3. Box and whisker plots show box denoting 25th and 75th percentiles with a line for 50th percentile (median), whiskers for 10th and 90th percentiles, and the dots representing 5th and 95th percentiles.

Sponsor's figure Four Month Safety Update Report Study 1321.3 page 16

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7.1.2. Secondary and Other Endpoints

The decrease of unbound dabigatran to near undetectable concentrations is shown in the sponsor's figure below for group A (serious bleeding, open circles) and group B (urgent surgery, closed circles). The x-axis shows time, i.e., the first 24 hours after idarucizumab administration and y-axis shows the concentration of unbound dabigatran (ng/mL). Idarucizumab was administered at time 0.

Figure 4. Decrease in Unbound Dabigatran in Study 1321.3

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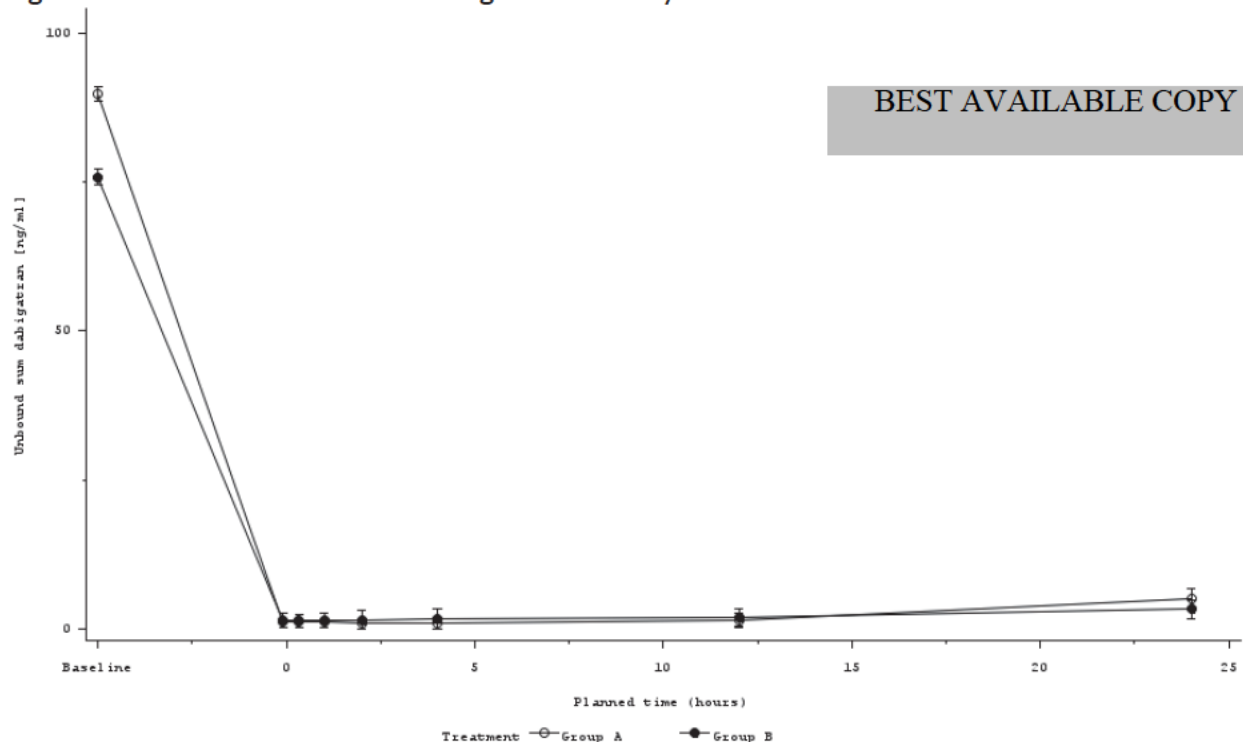
Group A, group B are not randomised groups, Unbound sum dabigatran concentration below BLQ is set to 1 ng/mL

Figure 15.2.2.3: 1 Geometric mean of unbound sum dabigatran concentration at planned time
Treated patients with PK measurement

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Sponsor's figure Four Month Safety Update Report Study 1321.3 page 19

The sponsor reported that in group A, bleeding cessation was determined by the physician in 48/66 (73%) of patients. Bleeding assessment was highly subjective. For 18/66 (27%) of patients no assessment of the bleed cessation could be made. The median time to bleeding stop was 9.8 hours (range: 0.2 h to 62 days). The assessment of bleeding stop was based upon whatever the investigator could visualize or measure. In Group B intra-operative status of bleeding was determined in 52 patients. For 48/52 (92.3%) of patients the surgeon judged there to be normal intra-operative hemostasis.

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Use of blood products was more frequent in Group A (serious bleeding) 45/66 (68%) of patients compared to Group B (urgent surgery) 23/57% (40%) of patients. The most frequently used product was packed RBCs, used in 51/123 (42%) of all patients. However, assessment of bleeding and the use of rescue therapy were highly subjective.

7.1.3. Subpopulations

Anticoagulant or antithrombotic therapy was re-started in 96 patients, i.e., 47/66 patients in Group A (serious bleeding) and 49/57 patients in Group B (urgent surgery). Dabigatran was re-started in 17/66 (25.8%) of the Group A patients and 34/57 (59.6%) of Group B patients. The re-start of dabigatran was preceded by bridging therapy in 8/17 patients in group A and 25/34 patients in group B. Bridging therapies primarily included low molecular weight heparin and unfractionated heparin. The median time to re-start of any anticoagulant therapy was 5 days for group A and 1 day for group B patients. Dabigatran re-start took 18 days in group A and 7 days in group B.

Reviewer comment for section 7. Maximal reversal (100%) of dTT was achieved in 39/40 (98%) of patients in group A (serious bleeding) and 26/28 (93%) of patients in group B (urgent surgery).   Maximal reversal (100%) of ECT was achieved in 42/47 (89%) of patients in group A and 30/34 (88%) of patients in group B. In patients treated with dabigatran in study 1321.3 the dTT and ECT decreased to normal levels within 10-30minutes of idarucizumab administration and are sustained for a period of 24 hours after the last dose of idarucizumab administration. The concentration of unbound dabigatran also appears to decrease with idarucizumab treatment. The assessment and management of bleeding in study 1321.3 was highly subjective. Therefore, changes in bleeding management are of unclear significance. The median time to re-start of any anticoagulant therapy was 4.6 days for group A and 1.3 days for group B patients. Dabigatran re-start took 18 days in group A and 7 days in group B. Differences in the time to restart of anticoagulant therapy may be due to the nature of serious bleeding compared to urgent surgery, i.e., a surgeon may feel that she/he has better control of the operative field and the wound in a surgical patient compared to a medical patient with bleeding from a source which is less obvious.

8 Review of Safety

8.1.   Safety Review Approach

A review of the safety database from study 1321.3 is presented in section 8 Review of Safety. In this study 123 patients previously treated with dabigatran who required rapid reversal of the anticoagulant effect of dabigatran emergency surgery/urgent procedures or had life threatening or uncontrolled bleeding were enrolled.

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8.2. Review of the Safety Database

Study 1321.3 is an ongoing, open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to adult 300 patients. The sponsor has enrolled 123 patients as of the April 1, 2015 cutoff date for the Four Month Safety Update Report. All 123 patients in this analysis received the pre-specified 5 g dose of idarucizumab. There were 66 patients in Group A (serious bleeding) and 57 patients in Group B (urgent surgery).

8.2.1. Relevant characteristics of the safety population:

Patients in study 1321.3 can be characterized as having serious medical conditions. In group A (serious bleeding group) there were 27/66(41%) who presented with gastrointestinal bleeding, 24/66 (36%) patients presented with intracranial bleeding, intracranial, the remaining 15/66 (22%) of patients had serious bleeding in other areas such as trauma, intramuscular, retroperitoneal, intra-pericardial, intra ocular and one bleeding location was not yet identified by the sponsor. Of the 57 patients in group B (urgent surgery group) surgery that was required in ≥ 3 patients was bone fractures 13/57 (23%) of patients, gall bladder disease (cholecystitis, cholelithiasis) 7/57 (12%) of patients, joint/wound infection 4/57 (7%) of patients and acute appendicitis, small bowel obstruction, bowel perforation in 3/57 (5%) each, respectively.

8.2.2. Adequacy of the safety database:

Patients enrolled in study 1321.3 can be expected to represent US patients. Patients of African-American or Asian descent appear to be under-represented in the study, i.e., 85% of patients enrolled in study 1321.3 as of the April 1, 2015 cutoff date are white. However, it is not expected that the coagulation cascade is different among these ethnic groups. As of the April 1, 2015 cutoff date 123/300 patients have been enrolled in study 1321.3.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Categorization of Adverse Events

AEs were graded and categorized according to MedDRA 17.0 criteria.

8.3.2. Routine Clinical Tests

Patients enrolled in study 1321.3 were monitored according to the study schedule shown in section 6 Review of Relevant Individual Trials Used to Support Efficacy in this review.

8.4. Safety Results

8.4.1. Deaths

There were 26 deaths among the 123 patients reported in the four month safety database, i.e.,

13 in Group A (serious bleeding) and 13 in Group B (urgent surgery). Thirteen of the deaths occurred in the first 5 days of the study. Patients who died before day 5 ranged in age from 69-93 years. Patients who died on or after day 5 ranged in age from 66-87. Causes of death are shown in the sponsor's table below. The causes of death appear to generally similar in the two groups of patients.

Table 8. Reported Causes of Death Study 1321.3

Patient Number	Age/Gender	Treatment Group	SAE that led to death (PT)	Days from treatment to Death
(b) (6)	82/Female	B	Cardiac arrest	<1
	93 / Male	B	Circulatory collapse	<1
	69/Male	A	Brain edema (ICH progression)*	1
	60 / Male	A	Respiratory failure	1
	77/Male	A	ICH progression	1
	81/Male	A	Aortic aneurysm rupture	1
	72/Female	A	Cardiogenic shock	1
	82/Female	B	Peritonitis, hemorrhagic anemia	1
	88/Female	B	Shock	1
	87 / Female	B	Septic shock	1
	60/Male	B	Sepsis, shock, GI hemorrhage	1
	87 / Male	B	Multi-organ failure	2
	69/Male	A	Cerebral hemorrhage progression	4

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Patient Number	Age/Gender	Treatment Group	SAE that led to death (PT)	Days from treatment to Death
(b) (6)	83/Female	A	Pulmonary edema	11
	87/Female	B	Cardiac failure acute	13
	78/Female	B	Cardiac arrest	21
	72/Female	B	Cerebral infarction	26
	73 / Male	A	Cardiac failure congestive	30
	76/Male	B	Pancreatic carcinoma	31
	73/Female	B	Pneumonia, septic shock	34
	83 / Male	A	General health deterioration	42
	80 / Male	A	Parkinson's Disease	43
	77/Male	A	Gastrointestinal hemorrhage	57
	86 / Female	A	Pneumonia	94
	80 / Male	B	Malignant neoplasm progression	101
	66/Male	A	Malignant neoplasm progression	106

Group A, patients with bleeding; Group B, patients requiring surgery.
*not yet coded
Sponsor table Four Month Safety Update Report page 26

8.4.2. Serious Adverse Events

In this study there were 53/123 (43%) of patients overall who reported serious adverse events (SAEs). The reviewer table below summarizes the SAEs that were reported in ≥ 2 patients in either treatment group.

Table 9. Serious Adverse Events in ≥ 3 Patients Study 1321.3

Preferred Term	Group A (Serious Bleeding) N = 66 N, %	Group B (Urgent Surgery) N =57 N, %	Total N= 123 N, %
Pneumonia	1, 2	1, 2	2, 2
Deep Vein Thrombosis	2, 3	1, 2	3, 2
Pulmonary Embolism	2, 3	0,0	2, 2
Acute Renal Failure	0, 0	2,4	2,2

Reviewer table derived from Sponsor Four Month Safety Update Report Study 1321.3 Sponsor table 15.3.1.1:4 pages 283-285

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8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no other AEs, other than those listed in section 8.4.1 Deaths that lead to dropouts or discontinuation of idarucizumab.

8.4.4. Significant Adverse Events

Treatment with an effective reversal agent in patients who are anticoagulated exposes the underlying thrombotic risk in such patients and increases the possibility that a thrombotic event will occur. There were 5 patients with thrombotic events during the study, 3 in Group A (serious bleeding) and 2 in group B (urgent surgery). These cases are described briefly below.

- Patient ___(b) (6)___, is a female age 86 years and experienced a non-ST elevation myocardial infarction 13 days after treatment with idarucizumab. No antithrombotic treatment had been re-started since the index event of an intra-cerebral bleed. Baseline conditions included atrial fibrillation, hypertension, previous stroke/transient ischemic attack (TIA) and the patient was hospitalized.
- Patient ___(b) (6)___, is a male age 85 years and entered in the study with an intracranial hemorrhage. The events of atrial thrombus, DVT and PE occurred starting 9 days after treatment with idarucizumab. During this time, the patient was hospitalized and no antithrombotic therapy had been re-started. This patient had concomitant conditions that included atrial fibrillation, diabetes, hypertension, and a prior left atrial thrombus.
- Patient ___(b) (6)___, is a female age 82 years who entered into the trial for surgery to treat cholecystitis. She had a history of hypertension, diabetes and previous stroke. Seven days after treatment with idarucizumab she developed a bilateral DVT. Imaging indicated that it was limited to below the knee. She was not receiving any antithrombotic treatment at the time of the event. At the end of the study, the DVT had not yet fully resolved.
- Patient ___(b) (6)___, is a male age 75 years who enrolled in the study for treatment of a gastrointestinal bleed. Two days after treatment, the patient was diagnosed with DVT and PE. He was not receiving antithrombotic therapy at that time. His medical history included Parkinson's disease. He was started one day later on heparin, then low molecular weight heparin, then re-started dabigatran 26 days later. He was not fully recovered from the pulmonary embolus at the end of the trial.
- Patient ___(b) (6)___, is a female age 72 years who entered into the study for surgical management of an infected left knee joint. The patient had a previous history of TIA. Twelve days after idarucizumab treatment, the patient experienced a rectal bleed on LMWH heparin, which was stopped. Twenty-four days after treatment the patient experienced an ischemic stroke (right middle cerebral artery infarction) and died 2 days later. The patient was not on any antithrombotic medication at the time of the event.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

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In study 1321.3 a total of 103/123 (84%) reported any AEs. AEs 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%).

8.4.6. **Laboratory Findings**

No significant changes in clinical laboratory values were observed in patients in either treatment group after idarucizumab therapy. Mean changes in hemoglobin, hematocrit, platelet count, liver function tests or creatinine clearance were not significantly altered after idarucizumab therapy over the course of the study.

8.4.7. **Vital Signs**

No significant changes in vital signs (temperature, blood pressure or heart rate) were noted after idarucizumab administration. Fluctuations in vital signs in the proposed indicated patient population, i.e., patients treated with dabigatran when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding, is not uncommon due to hemodynamic instability.

8.4.8. **QT**

Dr. Sahre states in the Clinical Pharmacology review (final signature date August 10, 2015) that idarucizumab is a fragment of a humanized murine monoclonal antibody with a molecular of weight 47 kDa, which will limit the ability of this compound to directly inhibit cardiac currents. No significant QT changes were noted on electrocardiogram testing.

8.4.9. **Immunogenicity**

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Sampling for anti-drug antibodies (ADA) against idarucizumab in study 1321.3 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). Not all patients were sampled for the development of antidrug antibodies (ADAs). Data are available for 47/123 patients with a pre-dose sample and at least one post-dose sample. The sponsor reports that 2 patients with baseline, non-specific ADAs (patients (b) (6) and (b) (6)) had persisting ADAs at day 30 day but the binding is not at the variable site. One more patient (patient (b) (6)) had a treatment emergent ADA at day 30 of mixed specificity.

8.4.10. Pediatrics and Assessment of Effects on Growth

Dabigatran is not approved in the US for use in pediatric patients. The sponsor requests a full waiver of the requirement for pediatric studies in 21 CFR Section 314.55 (a) that each application for a new dosage form contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indication in all relevant pediatric sub-populations. The sponsor states that idarucizumab is not likely to be used in a substantial number of pediatric patients treated with dabigatran who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required. The sponsor states that necessary studies are impossible or highly impractical because the number of such patients is low.

8.4.11. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no overdose or abuse potential for idarucizumab.

8.5. Safety in the Postmarket Setting

Idarucizumab is not marketed anywhere in the world.

8.5.1. Expectations on Safety in the Postmarket Setting

The sponsor requests waiver of the requirement for pediatric studies in 21 CFR Section 314.55 (a). Dabigatran is not approved in pediatric patients in the US. The sponsor states idarucizumab is not likely to be used in a substantial number of pediatric patients treated with dabigatran who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding

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requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required.

The sponsor should complete study 1321.3 and submit a final study report in order to support the application's full approval. Completion and submission of final study results for study 1321.3 will allow identification and assessment of any unexpected serious risk related to the use of idarucizumab in patients treated with dabigatran when rapid reversal of the anticoagulant pharmacodynamic effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

8.6. Additional Safety Issues From Other Disciplines

See Section 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety in this review. No additional safety issues have been identified from other disciplines.

Reviewer comment for section 8. Study 1321.3 is an ongoing, open label, multicenter, single arm, safety and efficacy trial in which the sponsor plans to enroll up to adult 300 patients. The sponsor has enrolled 123 patients as of the April 1, 2015 cutoff date for the Four Month Safety Update Report. All 123 patients in this analysis received the pre-specified 5 g dose of idarucizumab. There were 66 patients in Group A (serious bleeding) and 57 patients in Group B (urgent surgery). There were 26 deaths in the 123 patients reported in the four month safety database, i.e., 13 in Group A (serious bleeding) and 13 in Group B (urgent surgery). The mortality rate observed in study 1321.3 can be expected given the serious conditions of the enrolled patients in study 1321.3. Overall, SAEs reported in study 1321.3 in ≥ 2 patients included pneumonia, deep vein thrombosis, pulmonary embolism and acute renal failure. No significant differences were observed between treatment groups in terms of SAEs reported in study 1321.3. In addition, no significant changes in clinical laboratory tests, immunogenicity, QT evaluations.

The sponsor requests waiver of the requirement for pediatric studies in 21 CFR Section 314.55 (a). Dabigatran is not approved in pediatric patients in the US. The sponsor states idarucizumab is not likely to be used in a substantial number of pediatric patients treated with dabigatran who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required. The sponsor's request is reasonable and a full waiver of the requirement in 21 CFR Section 314.55 (a) should be granted.

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Overall, the benefit of idarucizumab to reverse the pharmacodynamic effect of dabigatran in patients who require emergency surgery/procedures or who have uncontrolled bleeding or life-threatening bleeding requiring urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is required is favorable. Significant safety risks have not been identified in this review.

9   Advisory Committee Meeting and Other External Consultations

An Oncology Drug Advisory Committee (ODAC) meeting or other external consultations are not recommended at this time.

10 Labeling Recommendations

10.1.   Prescribing Information

Key labeling idarucizumab labeling changes from a clinical perspective are discussed below. The sponsor's proposed wording is shown. My proposed wording additions are underlined and deletions are in strikethrough format. Additional labeling revisions are proposed by other review divisions which are presented in section 10.2 Patient Labeling and should be incorporated into the idarucizumab product label also shown below.

1. The sponsor's proposed indication is as follows. However, the proposed indication should be changed to remove the wording, "anticoagulant effect" and replaced with the wording "pharmacodynamic effect" which more accurately reflects that the effect of idarucizumab is on pharmacodynamic clotting parameters.

- Praxbind® (idarucizumab) is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran (~~p~~Pradaxa®) when ^(b) (4) reversal of the ~~anticoagulant~~ pharmacodynamic effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

2. The sponsor proposes the following wording in the Adverse Reactions Highlights section. ^(b) (4)

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                     ^{(b) (4)}. The sponsor should incorporate AEs that were observed in, e.g., ≥ 5% of normal healthy volunteers in studies.

-                     ^{(b) (4)}. In normal healthy volunteer studies the most frequently reported adverse reaction in greater than or equal to 5% of patients treated with idarucizumab was headache.

3. The sponsor proposes the following wording for the Adverse Reactions, Clinical Trial Experience section.   ^{(b) (4)}

-             ^{(b) (4)} Three clinical studies in healthy subjects have been completed, in which 224 were treated with idarucizumab. In these studies during the treatment period the overall frequency of adverse events was similar between idarucizumab treated subjects (55/224, 25%) and placebo treated subjects (26/105, 25%). Among those subjects treated with idarucizumab adverse events reported in greater than or equal to 5% of subjects was headache (12/224, 5%).

4. The sponsor proposes the following wording for the Clinical Studies section. However, the clinical studies should include a description of the treatments administered and key efficacy results of the studies.

- The safety and effectiveness of ~~TRADENAME~~ Praxbind   ^{(b) (4)}. Three clinical studies in healthy subjects have been completed, in which 224 were treated with idarucizumab. Subjects in these studies were pre-treated with dabigatran 220mg orally twice daily for three days followed by one additional 220mg dose of dabigatran on day four. Immediately after the administration of 5 g idarucizumab no anticoagulant activity as measured by dTT, ECT, aPTT, TT and ACT was observed. [see Pharmacodynamics 12.2].

                           ^{(b) (4)}

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(b) (4)

Following is the current draft labeling with proposed edits from the review team.

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10 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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10.2. Patient Labeling

Not applicable – no specific instructions for administration or use are directed at patients. This drug will be administered intravenously by a trained caregiver.

10.3. Nonprescription Labeling

Not applicable – idarucizumab is a prescription drug.

Reviewer comment for section 10. The sponsor should incorporate the reviewer proposed edits discussed in section 10.1 Prescribing Information and shown in section 10.2 Patient Labeling.

11 Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) is not recommended at this time.

12 Postmarketing Requirements and Commitments

I propose that the sponsor complete and submit a final study report for study 1321.3 as a Post Marketing Requirement in order to support the approval of idarucizumab. Completion and submission of final study results for study 1321.3 will allow identification and assessment of any unexpected serious risk related to the use of idarucizumab in patients treated with dabigatran when rapid

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reversal of the anticoagulant pharmacodynamic effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding.

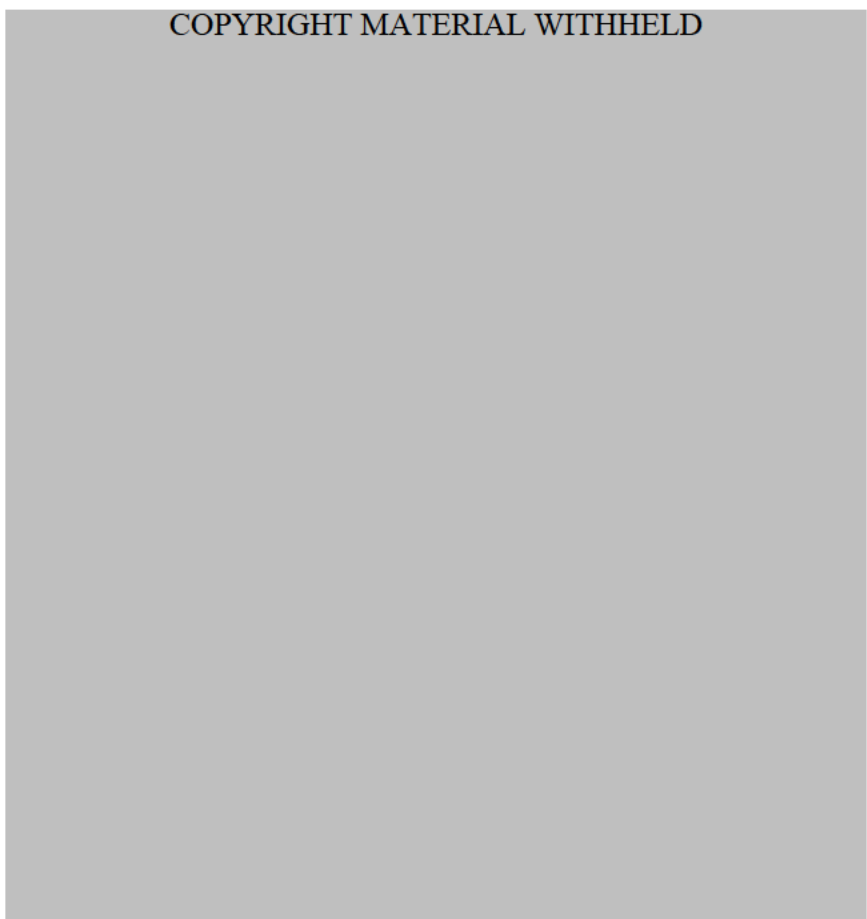# 13 Appendices

13.1.   References

- Pollack, C. V. et al.: Idarucizumab for dabigatran reversal. NEJM. 2015; 373(6): 511-520.

(b) (4). This published report is an interim analysis of study 1321.3 which evaluated 90 patients who received idarucizumab (51 patients with serious bleeding and 39 patients who required an urgent surgical procedure). Patients were enrolled from June 2014 to February 2015. Among 68 patients with an elevated dilute thrombin time and 81 with an elevated ecarin clotting time at baseline, the median maximum percentage reversal was 100% (95% confidence interval (CI): 100,100%) for each clotting test. The author's figure below shows the reversal of the dabigatran pharmacodynamic effect in patients treated with idarucizumab over time. The author states that the concentration of unbound dabigatran was reduced to a level at or near the lower limit of quantification in all but 1 patient. Subsequent increases in dabigatran concentrations that occurred 12 hours after the administration of idarucizumab in 6 patients and 24 hours after the administration of idarucizumab in 16 patients were also evident by increases in the clotting times and may reflect the redistribution of extravascular dabigatran into the intravascular compartment.

Figure 4. Reversal of Dabigatran Pharmacodynamic Effect by Idarucizumab (Pollack, 2015)

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Group A = patients with serious bleeding, Group B = patients who required urgent procedure
The author states that concentrations of unbound dabigatran remained below 20 ng per milliliter at 24 hours in 79% of the patients. Among 35 patients with serious bleeding hemostasis, as determined by local investigators, was restored at a median of 11.4 hours. Among 36 patients who required an urgent procedure normal intraoperative hemostasis was reported in 33 patients, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated. The author reported that 18/26 (70%) of patients died within <1-101 days after idarucizumab therapy of which 10/18 died within 4 days of idarucizumab therapy. Nine patients in each group died. The author concludes that idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran.

- Van Ryn, J. et al.: Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thromb. Hemost. 2010; 103:116-1127.

- Eerenberg, E.S. et al.: Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate. Circulation. 2011; 124:1573-1579.

- Hankey, G. J. and Eikelboom, J.W.: Dabigatran etexilate: a new oral thrombin inhibitor. 2011. Circulation. 123:1436-1450

13.2.   Financial Disclosure

Covered Clinical Study (Numbers): 1321.1, 1321.2, 1321.5 and 1321.3

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		

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Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): *Reviewer comment: No investigators listed with disclosable financial interests/arrangements.*		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:		
Significant payments of other sorts:		
Proprietary interest in the product tested held by investigator:		
Significant equity interest held by investigator in S		
Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 4		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Reviewer comment for section 13. The published interim report of study 1321.3 by Pollack (2015) includes 90 patients. The author concludes that that idarucizumab appears to be a safe and effective drug in patients treated with dabigatran when rapid reversal of

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the anticoagulant effect of dabigatran is required for emergency surgery/urgent procedures or in life threatening or uncontrolled bleeding. The author states that an increase in the dabigatran concentration was observed in 6 patients 12 hours after idarucizumab administration. The author states that it is uncertain whether patients with an increase in clotting time after previous recent idarucizumab therapy would benefit from additional idarucizumab treatment. No financial concerns have been uncovered in this review.