CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	August 13, 2015
Reviewer:	Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Acting Team Leader:	Naomi Redd, Pharm. D., DRISK
Acting Division Director:	Cynthia LaCivita, Pharm. D., DRISK
Subject:	Evaluation to determine whether a REMS is necessary to ensure that the benefits of idarucizumab outweighs its risks
Drug Name:	PRAXBIND (idarucizumab) Injection, for intravenous injection or infusion
Therapeutic Class:	Humanized monoclonal antibody fragment (Fab) reversal agent for the anticoagulant effect of dabigatran
Dosage, Form, Strength:	Idarucizumab injection for intravenous injection or infusion, 5.0 grams (g) provided as two separate 50 mL vials each containing 2.5 g idarucizumab
Office of New Drugs:	Division of Hematology Products (DHP)
Application Type/Number:	Rolling BLA 761-025 complete submission dated 02/22/15
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI)
PDUFA Deadline :	October 19, 2015
OSE RCM #:	2014-2601 NME, Master Record for Milestone Meetings 2014-2603 NME, DRISK REMS Review, Program Drug

Reference ID: 3806379

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APPENDIX

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for idarucizumab (Praxbind), a new molecular entity (NME), proposed for patients treated with Pradaxa (dabigatran) when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding in adults. This Rolling Biologic License Application (BLA) 761-025 was received across two submissions: non-clinical data was received on December 22, 2014/Sequence (Seq) 000 and clinical data was received on February 22, 2015 (Seq 001). The applicant submitted a proposed risk management plan (RMP) that does not include a REMS proposal. (b) (4)

The risks for idarucizumab include thrombotic events (of a patients underlying disease) when dabigatran therapy is discontinued and when idarucizumab reversal anticoagulant treatment is initiated, and potential hypersensivity reactions to idarucizumab. The DRISK and the DHP concurred that a REMS is not a needed to ensure the benefits outweigh the risks for risk management of idarucizumab. The DHP and the DRISK agreed that prescribers (i. e., emergency physicians, surgeons, hematologists, oncologists, internists) are informed on the serious risks associated with discontinuation of dabigatran treatment (Pradaxa labeling includes a BOX WARNING) when initiating an antidote for reversal of the anticoagulant effect of dabigatran. The DHP and DRISK concurred that the reported adverse events/reactions do not appear to be causally attributed to idarucizumab.

The prescription drug user fee act (PDUFA) goal date is October 19, 2015 (NME Priority review).

1 INTRODUCTION

The idarucizumab clinical development program is under Investigational New Drug (IND) 112-278 in the Division of Cardiovascular and Renal Products (DCRP) as a proposed therapeutic biologic formulation to bind to dabigatran and reverse its anticoagulant effects. The IND 112-278 was transferred from the Division of Cardiovascular and Renal Products (DCRP) to the DHP in 2014. The agency held a Pre-IND Meeting with Boehringer Ingelheim Pharmaceuticals, Inc (BIPI) on February 6, 2014 to discuss initiating clinical activities with BI-655075 (idarucizumab) in the United States (US) and gain agreement on what is required to support submission of an IND, and registration of BI-655075.

The proposed IND opening clinical trial was a prospective, uncontrolled, open-label (OL) study investigating the treatment of adult patients with 5 grams (g) of BI-655075, given as a regimen of 2.5 g + 2.5 g, with the second 2.5 g injection given no later than 15 minutes after the first 2.5 g of the dabigatran antidote. The Phase (P) 1 study 1321.1 in healthy male volunteers was completed in Europe. The proposed clinical development program for BI-655075 consists of the following clinical studies:

- 1321.1, P1 study (Belgium) in healthy adult male volunteers

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- 1321.2, P1 study (Belgium) in elderly volunteers and renally impaired patients, male and female
- 1321.3 study (37 countries[1]) as an uncontrolled case series clinical study of Reversal of the Anticoagulant Effects of Dabigatran by Intravenous Administration of 5.0 g Idarucizumab (BI-655075) in Patients Treated with Dabigatran Etexilate Who Have Uncontrolled Bleeding or Require Emergency Surgery or Procedures, i.e., a Study of the RE-VERSal Effect of Idarucizumab on Active Dabigatran (RE-VERS AD) Trial.

2 BACKGROUND

2.1 PRODUCT BACKGROUND

As explained by the applicant, idarucizumab is a humanized monoclonal antibody fragment (Fab) derived from an IgG1 isotype molecule directed against the thrombin inhibitor dabigatran. [2] The applicant claims that idarucizumab binds to dabigatran with approximately 300-fold higher affinity than the affinity of dabigatran for thrombin. [3] The high affinity of idarucizumab for dabigatran means any unbound dabigatran will preferentially bind to idarucizumab. As idarucizumab binds to dabigatran and its metabolites, idarucizumab neutralizes the dabigatran anticoagulant effect.[2]

According to the applicant, the Fab-dabigatran complex is characterized by a rapid on-rate and slow off-rate resulting in a stable long-lived complex.[2] The idarucizumab bi-exponential plasma concentration-time curves show a short initial plasma half-life of approximately 45 minutes and a longer terminal half-life of 5 to 11 hours.[4] Thrombin-bound dabigatran (or other plasma protein-bound dabigatran) will equilibrate with unbound dabigatran and rapidly become bound by any free idarucizumab. [2]

Because Idarucizumab is a Fab fragment without the Fc receptor binding fragment of an antibody, no complement-initiated cytotoxic effects or interactions with Fc_{γ}-receptors or neonatal Fc receptors are expected. At this time, idarucizumab is primarily intended for single use. [5]

The specific target of the idarucizumab clinical development program is to reverse the anticoagulant effect of dabigatran. Dabigatran etexilate (Pradaxa) is a direct thrombin inhibitor and potent anticoagulant that is the active principle of the prodrug, dabigatran

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[1] Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Great Britain, Hong Kong, Indi, Ireland, Israel, Italy, Japan, Korea, Latvia, Lebanon, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Russia, Singapore, Slovakia, south Africa, Spain, Sweden, Taiwan and the United States

[2] BLA 761-025 Praxbind (idarucizumab), Global Summit (GS), Section 2 Common Technical Document (CTD) Summaries, Module 2.2 Introduction, page 1 of 4

[3] BLA 761-025 Praxbind (idarucizumab), GS, Section 2, CTD Summaries, Module 2.5, Clinical Overview, Product Development Rationale, page 4 of 41

[4] BLA 761-025 Praxbind (idarucizumab), GS, Section 2 CTD, Module 2.5 Clinical Overview, page 8 of 41

[5] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.3 Summary of Clinical Efficacy, Drug Profile, page 8 of 67

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etexilate (DE). Dabigatran is approved for prevention or reduction of thrombotic events in the following patient populations:

- non-valvular atrial fibrillation;
- deep vein thrombosis (DVT) or pulmonary embolism (PE) who have been treated with a parenteral anticoagulant for 5 to 10 days;
- who have previously received anticoagulant therapy for treatment of venous thromboembolism; and

(b) (4)

Currently, Pradaxa is not approved in the US for use in pediatric patients. Though anticoagulant therapy is a mainstay of treatment and prevention of pathologic thrombosis in the adult patient populations cited above, bleeding remains a potential serious side effect associated with use of dabigatran.

Pre-Clinical Studies

The relevant species for assessing non-clinical toxicity of BI-655075 include the rat and Rhesus monkey. BI-655075 demonstrated rapid and complete reversal of dabigatran induced prolongation of tail bleeding time and associated ex vivo anticoagulant activity in a rat bleeding model.[6]

Only the Rhesus monkey studies were conducted to investigate toxicity in the presence of dabigatran. A target of 10-fold over the maximum anticipated human exposure, using a short 10 minute infusion was reported to be acceptable. The monkey studies revealed a similar dabigatran half-life in monkeys to that in humans of 6 to 10 hours, respectively, while the half-life in rats is ~ 1 hour. Following DE administration to monkeys, coagulation indices were elevated. Administration of idarucizumab neutralized the DE anticoagulant effect.[6]

Idarucizumab plasma levels and exposure were adequate to determine its toxicity after 4- and 2-week repeated administration to rats and monkeys, respectively, as maximum plasma and exposure levels of 7-fold and 3 to 5-fold those in healthy volunteers aged 45 to 64 years, respectively, were reached. Since idarucizumab binds dabigatran and dabigatran binds to thrombin, there is a theoretical possibility that anti-idarucizumab antibodies could bind to thrombin. Neither idarucizumab nor the presence of anti-idarucizumab antibodies had any effect on coagulation indices in rats or monkeys.[6] No adverse effect attributable to anti-idarucizumab antibodies were revealed in the rat or monkey.[6] Study in the rat and monkey demonstrated a lack of treatment-related adverse renal effects in rats and monkeys.[6]

Pregnancy Risks

Women of child bearing potential are instructed to avoid pregnancy during treatment with DE and it is recommended that the risks and benefits be weighed prior to use in pregnancy as animal studies have shown adverse effects on the fetus [reference: EU and

[6] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.5 Clinical Overview, Non-clinical Report, page 8 and pages 16 to 17 of 32

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USA labels for Pradaxa®]; consequently, no reproductive toxicity studies have been conducted with idarucizumab.[6] The applicant's proposed idarucizumab labeling includes (b) (4). The proposed idarucizumab substantially complete labeling includes a *Risk Summary* (Section 8.1 Pregnancy) that states, "There are no adequate and well-controlled studies of Praxbind in pregnant women to inform on associated risks."[7] These summarized non-clinical findings were confirmed with the Non-Clinical Reviewer, Emily Place, Ph. D., M. P. H.

2.2 Proposed Formulation and Dosage

The proposed to be marketed formulation for idarucizumab is developed for intravenous (IV) administration. (b) (4) .

Idarucizumab (50 mg/mL) is a clear to slightly opalescent, colorless to slightly yellow solution presented in a 50 mL glass vial (two 50 mL vials constitute one complete dose). The complete dose of 5 grams is administered IV, as two consecutive infusions (b) (4) or as a bolus injection.

2.3 Disease Condition – Rapid Reversal of Bleeding Events with Dabigatran required for Emergency Surgery/Urgent procedures and in Life-threatening or Uncontrolled Bleeding

One of the known serious risks of anticoagulant therapy is the lack of any approved treatment that directly reverses the anticoagulant effect of novel oral anticoagulants (NOACs)[9] including dabigatran. Dabigatran etexilate has been studied at two doses (110 mg and 150 mg) twice-a-day (b. i. d.) and in comparison to warfarin.

- For the prevention of stroke and systemic embolism in patients with atrial fibrillation, treatment with DE demonstrated superior efficacy over warfarin with the 150 mg bid dose with similar bleeding rates and non-inferiority with the 110 mg bid dose, with an improved bleeding profile (RE-LY, U09-3249-02). However, bleeding was a side effect in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial[10], with major bleeding reported in 3.3% and life-threatening bleeding in 1.5% of pts treated with DE 150 mg bid (yearly event rates).[11]

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[7] Pregnancy and Lactation Labeling Rule (PLLR) published December 4, 2014. Updated Labeling Review Tool issued August 2015.

[8] BLA 761025 Praxbind (idarucizumab), GS, Section 2 CTD summaries, Module 1.9.6 Other Correspondence Regarding Pediatric Exclusivity or Study Plans, Pediatric Study Plan, page 8 of 64

[9] NOAC products: Dabigatran (Pradaxa) Boehringer Ingelheim; rivaroxaban (Xarelto) Bayer Pharma /Janssen Pharmaceuticals; apixaban (Eliquis) Pfizer/Bristol-Myers Squibb; and edoxaban (Lixiana, Daiichi-Sankyo

[10] Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England journal of Medicine 2009, 361 (12):1139-51.

[11] BLA 761-025 Praxbind (idarucizumab), GS, Section 2 CTD, Module 2.5 Clinical Overview, page 4 of 41

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– In the RE-LY study in patients with atrial fibrillation (AF), the annualized rate of emergency surgery was 1.5% and 1.7% for DE 150 mg and DE 110 mg, respectively (RE-LY CTR U09-3249). Major bleeding rates in patients treated with DE 150 mg bid in RE-LY were approximately 3% per year (3 events per 100 patient years), of which half (1.5%) were categorized as life-threatening (RE-LY CTR U09-32449).[5]

In rare cases (0.2%), bleeding was fatal.[12] The rates of major and life-threatening bleeding in the other indications for dabigatran are lower than those seen in RE-LY due to a shorter average duration of treatment, a lower median age, and a lower rate of co-morbidities.[6]

2.4 ARMAMENTARIUM OF THERAPY FOR REVERSAL OF BLEEDING EVENTS WITH DABIGATRAN

At this time, there are no FDA-approved products that reverse the anticoagulant effect of dabigatran, any of the other NOACs, or warfarin. Anticoagulant therapy with novel oral anticoagulants (NOACs) [4] is used as an alternative therapy to Vitamin K antagonists such as warfarin, and low molecular weight heparins. Bleeding events are a potential serious adverse event (SAE) of treatment with NOAC therapy which includes dabigatran (Pradaxa).

One of the known serious risks of NOAC treatment is that there is no approved treatment that directly reverses the anticoagulant effect of NOACs including dabigatran. [13, 14]

2.5 REGULATORY HISTORY

The regulatory history specific to BLA 761-025 Praxbind (idarucizumab) follows:

- **August 4, 2011:** Pre-IND 112-278 Meeting was held for BI-655075 in the Division of Cardiovascular and Renal Products (DCRP).
  - The sponsor informed the agency that the clotting assays [e.g., activated partial thrombin time (aPTT), thrombin time (TT) or Ecarin clotting time (ECT)], as biomarkers of anticoagulation, will be employed to evaluate the primary efficacy endpoint (reversal of anticoagulant effects) in the BI-655075 clinical development program. The agency informed the sponsor that these biomarkers may be appropriate. However, at this time, the agency did not have adequate information to agree to any specific biomarker.
  - The agency reminded the sponsor to submit adequate plans to investigate the risk of immunogenicity of BI-655075 in humans.

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[12] Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J et al. Risk of bleeding with two doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the Randomized Evaluation of Long-Term anticoagulant Therapy (RE-LY) trial. Circulation 123, 2363 – 2372 (2011)

[13] Weitz JI, Quinlan DJ, Eikelboom JW. Peri-procedural management and approach to bleeding in patients taking dabigatran. Circulation 126 (20), 2428-2432 (2012)

[14] BLA 761-025 Praxbind (idarucizumab), GS, Section 2 CTD Summaries, Module 2.5 Clinical Overview, page 5 of 41

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- **January 31, 2013**: The BIPI sent responses to the agency on specific questions.

  The agency expressed concern about the precision of aPTT measurements as the most appropriate measure because the relationship between dabigatran plasma concentration and aPTT (fold change) is non-linear (insufficiently sensitive). The agency recommended that BIPI use the Ecarin clotting time as the biomarker to establish the primary endpoint as the relationship is linear (up to 400 ng/mL).

- **October 14, 2013**: The DCRP, Pre-IND Meeting focused on Chemistry and Manufacturing Controls for registration of two facilities. There was brief discussion on the bioanalytical strategy for detection of anti-BI-655075 antibodies and for differentiation between boosted anti-Fab anti-drug antibodies (ADA) and BI-655075-specific treatment emergent ADA in human plasma.

- **February 11, 2014**: DHP, Type B, Pre-IND Meeting. The agency provided the sponsor with responses on launching BI-655075 clinical studies in the US (Phase 1 study was completed in Europe). The agency underscored the need for the sponsor to include sufficient representation of both types of patients, i.e., those with bleeding and those requiring surgical intervention and collect all adverse events regardless of attribution.

  – There was brief discussion of the development of validated, drug-insensitive, *in vitro*, semi-quantitative assays for the measurement of anti-drug antibodies and neutralizing titers.

  – It was noted that no formal statistical testing is planned for evaluation of study 1321.3 (Interim Analysis and Final). The totality of data will be analyzed descriptively. Two subgroups of patients (bleeding patients and those requiring emergency surgery procedures) will be analyzed separately and pooled for overall conclusions.

- **February 14, 2014**: DHP, Pre-IND Meeting. The agency clarified to the sponsor that they have not provided sufficient justification to support re-institution of dabigatran therapy 24 hours after the last vial of antidote and after normal hemostasis has been achieved.

- **March 17, 2014**: On agreement of a Pediatric Investigation Plan, the European Medicines Agency (EMA) granted deferral for idarucizumab for study in pediatric patients. However, the EMA adapted idarucizumab to be developed for use in pediatric patients (aged birth to 18 years of age) who are treated with dabigatran who have uncontrolled or life-threatening bleeding which requires urgent intervention, or pediatric patients who require emergency surgery or procedures when rapid reversal of the anticoagulant effects of dabigatran is needed.

  – Note: Pradaxa was granted a full waiver of a pediatric assessment for the new active ingredient under the Pediatric Equity Act (PREA) requirements. The agency reached this conclusion because the necessary studies are impossible as this disease is rare in children. See Pradaxa NDA 022-512 Approval Letter (dated October 19, 2010).

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- **June 16, 2014**: The agency granted Breakthrough Designation for idarucizumab for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery/procedures when rapid reversal of the anticoagulant effects of dabigatran is required.
- **October 2014**: The agency indicated that they may consider approval based on a surrogate endpoint in volunteer trials for the assessment of clinical benefit of idarucizumab as a reversal agent for the anticoagulant effect of dabigatran..
- **November 13, 2014**: The DHP granted a waiver of Institutional Review Board requirements for use of idarucizumab in foreign investigational study, IND 112-278.
- **December 22, 2014**: BIPI submitted: 1) pre-submission contents of Rolling BLA 761-025 with non-clinical modules; 2) request for accelerated approval (per Pre-BLA meeting on October 14, 2014); 3) Priority Review as idarucizumab provides an improvement option in the treatment of serious or life-threatening clinical situations; and 4) Request for Proprietary Name Review (Praxbind received conditional approval on November 18, 2014.
- **February 20, 2015**: BIPI completed submission of the Rolling BLA 761-025 with Modules 1, 2 (2.2, 2.3, 2.5, and 2.7), 3, and 5. BIPI requested a full waiver of requirements under the PREA. BIPI included the European Union Pediatric Investigational Plan (including the pediatric protocol described in the Pediatric Investigational Plan with the pediatric study plan (required by the FDA). See above entry dated March 17, 2014.
- **May 18, 2015**: Idarucizumab was granted Orphan Drug Designation to reverse the anticoagulant effect of dabigatran due to uncontrolled life-threatening bleeding requiring urgent intervention or a need to undergo an emergency surgery/urgent invasive procedure.
- **June 16, 2014**: The agency granted Breakthrough Therapy designation to idarucizumab (BI-655075) for use in patients treated with dabigatran who have uncontrolled bleeding or who require emergency surgery procedures when rapid reversal of the anticoagulant effects of dabigatran is required meets criteria for Breakthrough Therapy designation. The agency initiated plans to expedite the manufacturing development strategy of idarucizumab.
- **May 15, 2015**: Idarucizumab Mid-Cycle Meeting in DHP. This reviewer summarized the applicant's RMP and shared that the DHP and DRISK concurred that, based on the reported risks with idarucizumab, a REMS is not needed at this time.
- **July 27, 2015**: The agency held the Late Cycle Meeting with the applicant.

2.2 Materials Reviewed

- **February 20, 2015**: Original BLA 761-025 Praxbind (idarucizumab) proposed for rapid reversal of the anticoagulant effect of dabigatran in adult patients when rapid reversal of the anticoagulant effect of dabigatran is required for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding in adults. This BLA includes a RMP (Module 1.16 Risk Management Plan).

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- **May 15, 2015**: BLA 761-025 Praxbind (idarucizumab) Mid-Cycle Review slides by Andrew Dmytrijuk, MD, Clinical Efficacy Reviewer, DHP
- **May 27, 2015**: Mid-Cycle Communication Meeting Minutes.
- **June 19, 2015**: BLA 761-025 Praxbind (idarucizumab), 120-Day Safety Update Report
- **July 8, 2015**: The DHP substantially completed proposed labeling.
- **July 20, 2015***:* Non-Clinical Review by Emily Place, Ph. D., M. P. H., Division of Hematology Oncology Toxicology (DHOT)
- **July 28, 2015***:* Pharmacology and Toxicology Idarucizumab Review by Christopher Sheth, Ph.D., DHOT
- **August 3, 2015**: Label and Labeling Review by Teresa Mcmillan, Pharm. D., DMEPA and Yelena Maslov, Pharm. D., Team Leader, DMEPA
- **August 10, 2015:** Clinical Biopharmacology Review by Martina Sahre, Pharm. D., DHP
- **August 12, 2015**: Substantially complete idarucizumab labeling
- *Pending:* Product Quality Review (Immunogenicity) by Lixin Xu, Ph. D.
- *Pending:* Office of Biopharmaceutical Products Review by Jibril Abdus-Samad, Pharm. D.
- *Pending:* Clinical Review of Idarucizumab by Andrew Dmytrijuk, M. D., DHP

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The efficacy and safety of idarucizumab (IDA)[15] solution for injection/infusion (50 mg/mL) proposed as a reversal agent for the anticoagulant effect of dabigatran in the setting of required emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding is derived from two Phase (P) 1 studies and one P3 study briefly summarized as follows:

- **Study 1321.1 (P1**) is a double-blind (DB), randomized (R), placebo-controlled (PBO-C) within dose groups, safety and reversibility [Pharmacokinetic (PK) and Pharmacodynamic (PD)] in healthy male volunteers.
  - **P**art 1: single-rising dose of IDA (20 mg up to 8 g)
  - Part 2: exploratory dose-finding with IDA (1 g, 2 g, 4 g) following pre-treatment of 220 mg DE twice-a-day (b. i. d.) for 3.5 days.

[15] Throughout Section 3, Overview of the Clinical Development Program, in this review, the abbreviation IDA represents idarucizumab and clotting laboratory tests are abbreviated as follows: diluted thrombin time (dTT), Ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and thrombin time (TT). Dabigatran etexilate will continue to be abbreviated as DE as appears earlier in this review. In this review, dabigatran is used for DE.

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- Part 2 + 3: IDA 5 g + 2.5 g or PBO, 1 hour (hr) apart, each as 5 minutes (mins) infusion with pre-treatment of 220 mg DE b.i.d. patients pretreated with DE for 3.5 days.

A total of 157 subjects were enrolled and 118 subjects were treated.

- **Study 1321.2 (P1)** is a DB, R, PBO-C, two-way cross over safety and reversibility (PK/PD) in volunteers, aged 45 to 64 years of age; elderly aged 65 to 80 years and in subjects with mild to moderate renal impairment. A total of 46 subjects were enrolled and treated. Idarucizumab or PBO: 1 g (elderly subjects, subjects with mild renal impairment), 2.5 g (healthy subjects aged 45 to 64 years, elderly subjects, subjects with mild renal impairment), 2 x 2.5 g (subjects with moderate renal impairment).
- **Study 1321.3 (RE-VERSE AD) [P3]** is a prospective, single cohort, open label case series clinical study in adult patients using IDA in patients treated with dabigatran and require emergency surgery or procedures for other morbidities and in patients who are taking dabigatran and present with life-threatening or uncontrolled bleeding. This study is planned to initiate > (b) (4) sites in up to 39 countries and is planned to recruit 200 to 300 patients over a 2 to 3 year period. This study was designed to verify safety and reversal effect in the target population. An interim analysis was planned after approximately 5 to 10% of the target total number of 200 to 300 patients were treated the cut-off date was December 2, 2014).
- **Study 1321.5 (P3)** is a DB, R, PBO-C within dose group safety and reversibility (PK/PD) in healthy Japanese male volunteers.
  - Part 1: single rising dose with 1 g, 2 g, 4 g IDA or PBO as 5 min infusion; 8 g IDA or PBO as 1 hr infusion
  - Part 2: 1 g, 2 g, 4 g IDA or PBO as 5 min infusion. Pre-treatment with 220 mg DE b. i. d. for 3.5 days (steady state of DE).

Disposition and Demographic Characteristics

- **Study 1321.3 Phase 3, Case Series Clinical Study**

Among 26 patients, 14 men and 12 women were treated with IDA. The mean age was 77.4 years and approximately one fourth of patients were at least 85 years of age. The mean basal metabolic rate was 26.5 mg/m^2. All 26 patients were being treated with DE for atrial fibrillation.

The majority of the 26 patients (81%) had hypertension, ~ 35% had congestive heart failure, ~ 35% had diabetes; ~ 23% had coronary artery disease, and ~ 19% had a prior stroke/transient ischemic attack (all 5 of these patients were in Group A). All 26 patients reported a concomitant medication at baseline. The most common classes of concomitant medications were HMG CoA reductase inhibitors (statins, taken by 53.8% of treated patients), proton pump inhibitors (50.0%), anilides (paracetamol) and beta blockers (each class taken by 46.2% of patients), and sulfonamides (42.3%).

The majority of 26 patients (69.2%) received 110 mg DE bid and 30.8% received 150 mg DE bid. Among the 26 treated patients, approximately 42% of patients received the last dose of DE <12 hours before starting IDA treatment; another 39% received the last dose

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of DE < 24 hours before starting IDA, and approximately 19% received their last DE between 24 and 48 hours before starting IDA.

For the 11 treated patients in Group A who had a bleeding event requiring IDA treatment, 6 had a GI bleed and 5 had an ICH. One patient (# (b) (6)) had an intra-cranial hemorrhage also reported as due to trauma and was counted in these 2 categories.[16] The DHP Clinical Reviewer agrees with these results.

Efficacy Results

- **Study 1321.1: Results of the Effect of IDA on Dabigatran PK and PD**

The effect of IDA on unbound dabigatran concentration was dose-dependent PK, where the mean concentrations of unbound dabigatran remained < 20 ng/mL after infusion of 1 g IDA, < 10 ng/mL after infusion of 2 g IDA, and < 5 ng/mL after infusion of higher IDA doses over the observation period. The DHP Clinical Reviewer and the DHP Clinical Pharmacology Reviewer agree with these results. The PD for IDA demonstrated:

– 1 g IDA showed immediate and complete reversal with partial return of the sum dabigatran anticoagulant effect starting between 30 minutes (mins) to 2 hrs after the end of the infusion. This result is based on diluted thrombin time (dTT), Ecarin clotting time (ECT), activated partial thromboplastin time (aPTT), and thrombin time (TT).

– 2 g IDA dose resulted in immediate, complete, and sustained reversal with the clotting assays dTT and aPTT while the mean ECT and TT values were slightly above the upper limit of normal (ULN) from 6 to 16 hrs and 2 to 24 hrs after the end of the IDA infusion.

– 4 g IDA showed immediate, complete and sustained reversal with dTT, ECT and aPTT; TT values were slightly above the ULN from 12 to 24 hrs after the end of the IDA infusion.

– 5 g + 2.5 g IDA resulted in immediate, complete, and sustained reversal with dTT, ECT, aPTT, and TT.

The administration of (≥ 2 g) IDA resulted in immediate, complete, and sustained reversal of dabigatran based on dTT and aPTT. In the absence of dabigatran, IDA had no apparent effect on clotting parameters.

- **Study 1321.2: Results of the Effect of IDA on Dabigatran PK and PD**

The primary endpoint was reversal of dabigatran-induced prolongation of blood coagulation times.

– **PK**: After the end of the infusion of all IDA doses and in all populations (including renal impairment) unbound dabigatran plasma concentrations decreased to or below the lower limit of quantification of 1 ng/mL, concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The duration of the effect on IDA on unbound sum dabigatran concentrations increased with dose. When higher IDA doses

[16] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.3 Summary of Clinical Efficacy, page 29 of 67

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(2.5 g or 5 g) were infused, geometric mean concentrations of unbound sum dabigatran remained below11 ng/mL for the observation period.

– **PD**: Complete reversal of individual dabigatran-induced clotting time prolongation within 10 mins after the end of IDA infusion was observed for all patients of all dose groups for the clotting parameters dTT and ECT (primary analysis) and for aPTT and TT. The PBO infusion had no effect on the clotting parameters. . Infusion of a total dose of 5 g IDA resulted in sustained reversal of dabigatran-induced clotting time prolongation over the entire observation period in healthy subjects (45 to 64 years of age), healthy elderly (65 to 80 years of age), and subjects with mild renal impairment.

  The reversal effect of IDA was similar in male and female subjects. A second dose of IDA was safe, well tolerated, and effective. The dabigatran can be restarted 24 hrs after IDA treatment.

- **Study 1321.5: Results of the Effect of IDA on Dabigatran PK and PD**

In the absence of dabigatran, IDA had no apparent effect on clotting in healthy Japanese male volunteers. Immediate and complete reversal was observed on the basis of the unbound fraction of sum dabigatran and coagulation parameters of dTT, ECT, TT and aPTT following administration of IDA at steady state of dabigatran in all dose groups. During IDA infusion, a rapid and substantial-decline of unbound sum dabigatran concentrations to at least the lower limit of quantitation, 1 ng/mL) was observed, concomitantly with abolished or nearly abolished dabigatran anticoagulation activity. The reversal effect was sustained at 4 g and the proposed therapeutic dose of 2.5 g + 2.5 g. See the DHP Clinical Biopharmacology Review by Martina Sahre, Pharm. D., with details on these results.

- **Study 1321.3 Efficacy in the Case Series Clinical Study (Interim Analysis)**

The primary endpoint of P3 study 1321.3, RE-VERSE AD, is reversal of the anticoagulant effect of dabigatran, based on a central laboratory assessment of Ecarin clotting time (ECT) and diluted thrombin time (dTT) as biomarkers. Other coagulation tests (Thrombin Time (TT), activated partial thrombin time (aPTT) were also measured. Clinical events were recorded; however, this trial has only a single cohort. The DHP and the BIPI agreed that given the potential life-threatening condition of some patients considered for enrollment, it was not ethical to establish a control group who would not receive the antidote.[17]

Patients were only evaluable for reversal of a PD coagulation marker if their baseline value was above the ULN for the respective biomarker (110% ULN for the primary endpoint). See the DHP Clinical Review.

3.1 CLINICAL SAFETY

A total of 283 treated patients were treated across the three P1 studies. Trials 1321.1 and 1321.2 were conducted in Belgium at the same clinical site and the single-center study 3121.5 was conducted in Japan. The interim analysis of the ongoing P3, clinical case

[17] BLA 761-025 Praxbind (idarucizumab), GS, Seq. 010, Clinical Safety Update, page 7 of 887

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series (1321.3) safety, PK and PD study includes the first 26 patients treated with IDA (cut-off date of 02Dec2014).

Disposition

Approximately half of the 283 treated subjects who participated in study 1321.1 (157 subjects), about one-sixth (46 subjects) participated in the crossover trial 1321.2, and about one-third of the subjects (80 subjects) were included in the Japanese trial 1321.5 (see **Table 1**). A total of 224 patients were treated with IDA and 105 patients received PBO (regardless of DE pre-treatment). Study 1321.1 contributed 52.7% of patients to the treatment group IDA/DE+IDA while similar proportions of patients from studies 1321.2 and 1321.5 were treated with IDA/DE + IDA.[18] A total of 141 of 283 patients received pre-treatment with DE.

A total of 46 treated subjects in the crossover trial 1321.2 study were pretreated with DE before infusion of IDA or PBO. Thirty percent (30%) (1321.1 study) and 60% (1321.5 study) of the subjects, respectively, received pre-treatment with DE. **Table 1** shows the total number of subjects, by treatment arm, in studies 1321.1, 1321.2, and 1321.5.

Table 1. Number of Treated Subjects for Studies 1321.1, 1321.2 and 1321.5

		PBO		IDA		Total		
	DE N (%)	PBO alone N (%)	DE + PBO N (%)	IDA alone N (%)	DE + IDA N (%)	PBO/ DE+PBO N (%)	IDA/ DE+PBO N (%)	Overall N
Tx pts in pooled P1 studies	141 (100)	35 (100)	70 (100)	107 (100)	117 (100)	105 (100)	224 (100)	283
1321.1	47 (33.3)	27 (77.1)	12 (17.1)	83 (77.6)	35 (29.9)	39 (37.1)	118 (52.7	157
1321.2	46 (32.6)	0	46 (65.7)	0	46 (39.3)	46 (43.8)	46 (20.5)	46
1321.5	48 (34)	8 (22.9)	12 (17.1)	24 (22.4)	36 (30.8)	20 (19)	60 (26.8)	80
Pts from crossover trial 1321.2 are counted more than 1 treatment group but only once in overall column.								
All pts in 1321.2 and some pts in 1321.1 and 1321.5 were pretreated with DE before infusion of IDA/PBO.								

Reference: BLA 761-025 Praxbind (Idarucizumab), GS, Module 2.7.4 Summary of Clinical Safety, Table 1.2.1.1:1, page 26 of 83

Exposure

In the pooled Phase 1 studies, the most frequently employed dose of idarucizumab (IDA/DE+IDA) was in the range of ≥ 1 g to < 2.5 g for 41.1% of all subjects, followed by ≥ 2.5 g to < 5 g IDA for 21% of subjects. Similar proportions of subjects received 5 g IDA (15.6%) or higher doses of > 5 g to 8 g IDA (12.1%) based on all subjects receiving IDA with or without DE pre-treatment.[19]

[18] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.4, Summary of Clinical Safety, page 26 of 83

[19] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.4 Summary of Clinical Safety, page 28 of 83, including Table 1.2.2.1:1 on page 28 of 83

Reference ID: 3806379

In clinical case series, study 1321.3, all 26 patients received both vials of IDA. The mean time since the last DE dose to the time of 1st IDA administration was 17.68 hrs (Group A) and 17.43 hrs (Group B). The mean time for administration of the 1st and 2nd vials was slightly longer for Group A (1st vial 6.73 min, 2nd vial 7.36 mins) compared with Group B (1st vial 5.87 mins, 2nd vial: 5.73 mins).

3.1.1 Clinical Safety Results - Pooled Phase 1 Studies in Healthy Volunteers

Study 1321.1: No deaths were reported in this study. The most common adverse events during pre-treatment of DE were pre-syncope (5 subjects, 10.6%) and headache (4 subjects, 8.5%). The frequency of AEs was higher in the PBO group (12 subjects, 44.4%) than in the DE + PBO group (2 subjects, 16.7%). Headache, nasopharyngitis, and skin irritation (each 2 subjects, 7.4%) were the most frequently reported AEs in the PBO groups without DE pre-treatment. Headache, infusion site hematoma and oropharyngeal pain (each 1 subject, 8.3%) were most commonly reported in eh DE + PBO group.[20]

In the IDA treatment groups (IDA/DE + IDA), the most frequently reported AEs were headache (9 of 118 subjects), nasopharyngitis (6 of 118 subjects), skin irritation (6 of 118 subjects), and back pain (5 of 118 subjects).[17] The DHP Clinical Reviewer concurs that the majority of AEs were of mild intensity and none were of severe intensity. There did not appear to be a dose relationship to IDA and any of the reported AEs.

During the treatment period, there were no deaths, no serious adverse events (SAEs), no AEs leading to discontinuation causally related to IDA. During long-term follow-up, 1 subject (20 mg IDA) was reported with a SAE viral infection (moderate intensity, requiring hospitalization). The event was not causally attributed to IDA and the subject recovered.[17] Idarucizumab showed a low level of immunogenicity with 7-treatment emergent anti-IDA antibody responses in 118 subjects treated with IDA.

Study 1321.2:

No deaths were reported in this study. The reported AEs were all mild intensity. There was no dose relationship to IDA of any AE observed. There did not appear to be a clinically relevant difference in AEs in male and female volunteers (with and without renal impairment) receiving IDA compared with PBO. The reported AEs with IDA did not show any unexpected safety findings and showed no clinically relevant safety concerns. Treatment with IDA showed a low level of immunogenicity with 5 of 46 IDA-treated subjects who had treatment-emergent anti-IDA antibody responses. The DHP Clinical Reviewer concurs.

Study 3121.5 (Japan)

No deaths were reported in this study. One subject of 32 subjects (3.1%) treated with PBO (5 min infusion) was reported to have an increased blood creatinine phosphokinase. The elevation in creatinine kinase returned to normal at follow-up visits. The event was assessed as mild intensity and possibly drug-related. One subject in Part 1 and 2 showed a dose-dependent increase in low molecular weight proteins and urine proteins that

[20] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.3 Summary of Clinical Safety, page 20 of 83

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returned to normal with 4 to 12 hrs after the end of the IDA infusion. No further AEs were reported in this study.

The IDA infusion (doses from 1 g to 8 g) at the steady state of DE was safe and well tolerated in healthy Japanese subjects. The substantially complete labeling cites the most frequently reported adverse reaction (greater than or equal to 5%) of patients treated with IDA as headache. Treatment with IDA showed a low level of immunogenicity with 4 out of 20 patients (who had both pre-treatment and during antidote therapy) with treatment-emergent anti-IDA antibodies. See the DHP Clinical Review for additional details.

3.1.2 Clinical Safety Results - Interim Analysis, P3 study 3121.3

Study 1321.3

All 26 treated patients received both vials of IDA (Group A, bleeding events: 11 patients, and Group B, requiring surgery: 15 patients). Due to the small number of patients in this interim analysis, an AE reported in one patient would be counted as having occurred in > 5% of patients in either group. Baseline morbidity in these patients treated with dabigatran make it challenging to reach a clinically meaningful conclusion in this small study population.

Deaths

During the treatment period, 3 patients died and the fatalities were not considered causally related to IDA. As of the cut-off date of December 2, 2014 a total of 9 deaths were reported (Group A, 5 patients; and Group B, 4 patients). No deaths were causally attributed to the administration of IDA and 3 of these 9 deaths were reported during the treatment period.

- One patient ([redacted] (b) (6)) died ~ 7 hrs after the start of treatment; however, the gastrointestinal bleeding, for which the patient was enrolled in the study, began prior to administration of the IDA. Therefore, this death was classified as during screening.
- 4 patients died within 1 to 2 days after IDA treatment. The SAEs causally attributed to these deaths were circulatory collapse, death, multi-organ failure, and septic shock.
- 5 deaths occurred 1 to 3 months after IDA treatment due to infection or co-morbidities (congestive heart failure, general physical deterioration, Parkinson's disease, pneumonia, and progression of malignant neoplasm. See the **Appendix**, to this review, **Table 2** with the SAE associated with each of these 9 fatalities.

A total of 18 patients (69.2%) were reported with AEs. Of these 18 patients, 9 patients (50%) were in Group A (uncontrolled bleeding) and 9 patients (50%) in Group B (requiring surgery). The majority of AEs were mild in severity and include many system organ classes (SOC), i.e., cardiac, respiratory, nervous, skeletal, metabolic and vascular. The most frequent SOCs were general disorders and administration site conditions (5 patients, 19.2%), cardiac disorders (4 patients, 15.4%) and infections and infestations (4 patients, 15.4%). Non-serious AEs were mild to moderate in severity. No AEs led to discontinuation of IDA. See **Table 3** with AEs across severity categories in study 1321.3.

Serious Adverse Events

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A total of 5 patients (19.2%) had reported SAEs during the IDA treatment period: one patient (9.1%) in Group A and 4 patients (26.7%) in Group B. The applicant reported one patient (# (b) (6)) in Group A with the SAE, uncontrolled bleeding: an 85-year old male with traumatic subarachnoid hemorrhage, SAEs of atrial thrombus, deep vein thrombosis, and pulmonary embolism, all of which could be considered causally attributed to IDA. Thrombotic events were reported in 2 patients in Group A (on Day 9 and Day 13, respectively), after IDA exposure in the absence of the antithrombotic treatment with dabigatran.

Table 3. Adverse Events for Study 1321.3 during IDA treatment

	Group A N (%)	Group B N (%)	Total N (%)
# Pts	11(100%)	15 (100%)	26 (100%)
Pts with any AE	9 (81.8)	9 (60)	18 (69.2)
Pts with severe AEs	2 (18.2)	4 (26.7)	6 (23.1)
Pts w/investigator defined IDA related AEs	1 (9.1)	0	0
Pts w/SAEs	1 (9.1)	4 (26.7)	5 (19.2)
Fatal	0	3 (20)	3 (11.5)
Immediately life-threatening	0	0	0
Prolonged hospitalization	0	1 (6.7)	1 (3.8)
Other	1 (9.1)	0	1 (3.8)
Abbreviations: # - Number; Pt-patient; w-with			
Ref: BLA 761-025 Praxbind, GS, Module 2.7.3 Summary of Clinical Safety, Table 2.1.5.1:1, page 54 of 83			

Common Adverse Events

During the treatment period, the most common AEs on IDA (IDA/DE+IDA) were headache (12 subjects, 5.4%), skin irritation (6 subjects, 2.7%), dizziness (5 subjects, 2.2%), and back pain (4 subjects, 1.8%). The most frequent reported AEs after infusion of PBO (PBO/DE+PBO) were headache, skin irritation, back pain, nasopharyngitis, epistaxis, and chest pain which were reported for 2 subjects each (1.9%). All other AEs reported after infusion of IDA were similar to those reported for PBO-treated patients. The substantially completed proposed labeling reports adverse reactions in greater than or equal to 5% of patients treated with IDA as headache. See labeling Section 6, Adverse Reactions.

3.2 RISKS OF SPECIAL INTEREST

Bleeding

Adverse events related to bleeding are the following: epistaxis occurred with higher frequencies in the DE pre-treatment (2.1%) and PBO/DE+PBO (1.9%) groups than in the

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IDA/DE_IDA group (0.4%). Other AEs related to bleeding, i.e., gingival bleeding, ecchymosis, and infusion site hematoma, were documented only for 1 patient each in the DE+PBO group (1.4%) and for none of the IDA-treated patients. Injection site hematoma was reported with almost identical frequencies in the PBO/DE+PBO (1.0%) and IDA/DE+IDA (0.9%) groups. The DHP Clinical Reviewer concurs with these results.

Hereditary Fructose Intolerance

Sorbitol may not be of major concern for the general population; however, sorbitol could be of concern for persons with the rare condition of Hereditary Fructose Intolerance.[21] The amount of parenteral sorbitol delivered with the recommended dose of 5 g idarucizumab is approximately 4 g. Some patients with hereditary fructose intolerance may not be able to tolerate this dose.

Per the applicant's proposed labeling, in patients with hereditary fructose intolerance, parenteral administration of sorbitol has been associated with reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory and synthetic function and death (see proposed labeling, *Section 5, Warnings and Precautions, Subsection 5.4 Hereditary Fructose Intolerance).* As confirmed with the DHP Clinical Reviewer, information about the potential risks associated with use of idarucizumab in persons with Hereditary Fructose Intolerance will be included in labeling.

Restarting Antithrombotic Therapy

Patients being treated with dabigatran therapy have underlying disease conditions that predispose them to thromboembolic events. Reversing dabigatran anticoagulant therapy exposes these patients to thrombotic risks of their underlying disease including bleeding events (intracranial hemorrhage, gastrointestinal hemorrhage). To reduce this risk, resumption of anticoagulant therapy needs to be considered as soon as medically appropriate after idarucizumab treatment. See the proposed labeling: Section 2, Dosage and Administration; Section 5, Warnings and Precautions; and Section 17, Patient Counseling Information for additional details).

Hypersensitivity Reactions

See the 120-Day Safety Update Report with updated information on the Interim Analysis (study 1321.3) of hypersensitivity reactions.

Anti-Idarucizumab Anti-Drug Antibodies

Because BI 655075 is a humanized monoclonal antibody fragment derived from an IgG1 isotype molecule directed against the thrombin inhibitor dabigatran, it is unlikely to result in immune complex formation in the absence of antidrug antibodies (ADA). Immuno-assay methods for the detection and characterization of anti-idarucizumab antibodies were developed and validated for human plasma at (b) (4)

[21] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.4 Non-Clinical Overview, page 18 of 26

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There did not appear to be a correlation of antibody development to the frequency of AEs in any of three P1 studies. See brief comment on the development of ADAs in the clinical safety report for each P1 study. A total of 18 of 224 subjects (8%) treated with idarucizumab in studies 1321.1, 1321.2, and1321.5 had treatment-emergent anti idarucizumab antibody responses. A total of 9 of these subjects had transient responses, and 9 patients had what were characterized as possibly persistent responses.

In total, 43 of 574 samples (7.5%) across the P1 studies 1321.1, 1321.2, and 1321.5 were confirmed positive with the modified TT assay. In each trial, some subjects had positive responses at the pre-dose visit (overall 10 of 141 subjects, 7.1%), and these were considered to be false positive. The screening threshold value for this assay was set with a target false positive rate of 5%. The individual TT results were almost always very close to the threshold value. Taken together, this indicates the absence of relevant levels of anti-dabigatran antibodies.[22] The impact of potential anti-dabigatran antibodies on the effectiveness' of subsequent dabigatran appears to be minimal. See the DHP Clinical Review for additional details on the impact of anti-dabigatran antibodies.

Secondary to the required long-term follow-up time, anti-drug antibodies in P3 study, 1321.3, are not complete but show a low level of immunogenicity. See the DHP Clinical Review for details on these interim results.

3.3 120-DAY SAFETY UPDATE REPORT

The 120-day Safety Update Report (SUR) on idarucizumab was submitted on June 19, 2015. The 4-Month Safety Update Report (SUR) includes interim analysis data from 123 dabigatran-treated patients recruited to RE-VERSE AD up to April 1, 2015, including 26 patients reported in the interim analysis filed under BLA 761-025.

- A total of 123 patients were treated with 5 g dose of idarucizumab. A total of 66 patients in Group A (bleeding) and 57 patients in Group B (surgery) are reported.
- A total of 2 patients (after the cut-off date) received a second 5 g dose of idarucizumab within 24 hours. These two patients are not included in the reported 123 patients but are important to the DHP in understanding idarucizumab and potentially a second dose of 5 g idarucizumab due to re-bleeding. The DHP is interested in a second idarucizumab dose administered at weeks, months or years later to understand potential immune responses. These two cases of repeat idarucizumab exposure (during one hospitalization) showed clinical information in which a second idarucizumab dose was effective by anticoagulation tests in stopping bleeding. See the DHP Clinical Review for details reported in the 120-Day SUR.

From June 2014 to April 1, 2015, 123 patients were enrolled from 219 activated sites in 35 countries including 5 patients from 26 US sites. The goal of this study is to enroll 200 to 300 patients.[23] The more activated sites participating in the study improves the likelihood for increased patient enrollment. The demographics of this population (RE-VERSE-AD) are comparable with the demographics of patients from the RE-LY trial.

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[22] BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.4 Summary of Clinical Safety, page 66 of 83

[23] BLA 761-025 Praxbind (idarucizumab) GS, 120-Day Safety Update Report, page 8 pf 887

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The median age is 77 years, slightly older than the average age of 71.5 years in the RE-LY trial. Renal function is lower than in the RE-LY trial where the median creatinine clearance (CrCl) for all patients was 68.4 mL/min compared to 55.1 mL in this study. In RE-VERSE-AD, bleeding patients (Group A) had slightly worse renal function (median CrCl = 52.7 mL/min) compared to the surgical patients (Group B, 57.3 mL/min). The most common dabigatran dose is 110 mg bid (65% of patients).

Idarucizumab Dose Timing

Median time between the last dose of DE and the start of the 1st vial of idarucizumab was 15.6 hours (ranging from 1.5 hrs to ~ 94 hours). These data are patient reported. Approximately 1/3 of patients took their last dose of dabigatran less than 12 hours prior to idarucizumab with 37% having the last dose between 12 and 24 hours and 26% between 24 and 48 hours.

Co-Morbidities

Patients treated with idarucizumab had high frequency of co-morbidities. As agreed with by the DHP Clinical Reviewer, the frequency of risk factors associated with bleeding and stroke risk in patients with atrial fibrillation included: hypertension (77%), heart failure (39%), diabetes (27%), coronary artery disease (31%), previous history of stroke (28%), previous history of transient ischemic attack (TIA), 11.4%, and previous history of systemic embolism (8.9%). Prior major bleed was reported in 4% and active cancer was reported in 11%.

Group A - Bleeding Events

Based on the Internal Society for Thrombosis and Hemostasis (ISTH) classification of bleeding, 63 of 66 bleeds were classified as either major or major and life-threatening. A total of 47 bleeds were considered severe or life-threatening and 14 were evaluated as moderate.[24]

Group B - Surgery

There were 57 patients allocated to the surgery/invasive procedure group. Three of these 57 patients did not undergo planned surgery in Group B:

- 1 patient (b) (6) had taken an overdose of dabigatran (~125 capsules). During preparation for dialysis, the patient was treated with idarucizumab clotting tests normalized and dialysis was subsequently cancelled.
- 1 patient (b) (6) with acute mesenteric ischemia, was treated with idarucizumab, but was too unstable to undergo planned exploratory laparoscopy. This patient died 1 day later due to circulatory collapse.

[24] Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries Definition for Bleeding (GUSTO) Scale for Bleeding: Severe or life-threatening (intracerebral hemorrhage; resulting in substantial hemodynamic compromise requiring treatment); Moderate (requiring blood transfusion but not resulting in hemodynamic compromise); Mild (bleeding that does not meet the above criteria) by Mehran R, Rao SV, Bhatt DL, Gibson CM et al. (2011) Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium Circulation 123 (23): 2736-47.

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– 1 patient (b) (6) was scheduled to undergo gastric perforation repair and was treated with idarucizumab. However, the patient was too unstable for surgery. She died 1 day later of peritonitis and acute post-hemorrhagic anemia.

Central Laboratory Data

Only 90 of 123 patients in this interim analysis had central laboratory data reported in the 120-Day SUR. There were 3 cases of elevated liver enzymes with increased bilirubin. These cases were confounded and the elevated liver enzymes and bilirubin results were not causally attributed to idarucizumab. See the Clinical Review for additional details.

Patient Disposition

Of the 123 patients in the interim analysis, 32 (26%) remain in follow-up with a minimum of 1 month observation. A total of 62 (50.4%) of the remaining 91 patients completed 3 months of observation.

Efficacy

Each patient serves as their own control so that an extent of reversibility can be calculated. Per the applicant, "at entry, the dilute TT was normal in 22 patients, of whom 9 also had normal ECTs. Therefore, percentage reversal of either test with idarucizumab could be determined in 68 (40 in Group A and 28 in Group B) and 81 (47 in Group A and 34 in Group B) of the 90 patients, respectively.[25]

The maximum reversal of ECT or dTT in the 1st 4 hours was the primary endpoint. The median maximum reversal in Group A and B patients was 100% [95% Confidence Interval (CI)], 100-100) for both the dilute TT and ECT. The narrow confidence interval is based on the fact that more than 89% of patients achieved complete reversal. The reversal was reported immediately after administration of the 1st vial.[15]

Normalization of clotting tests is defined as those tests with values equal to or below the upper limit of normal. The dilute TT was normalized in 97.5% and 92.9% of evaluable patients in Groups A and B, respectively, whereas the ECT was normalized in 89.4% and 88.2% of evaluable patients in Groups A and B, respectively.[15]

Anticoagulant or antithrombotic therapy was re-started in 96 patients (47 in Group A and 49 in Group B). Dabigatran was re-started in 17 (25.8%) of the Group A patients and 34 (59.6%) of the Group B patients. Dabigatran re-start was preceded by bridging therapy (i. e., low-molecular weight heparin, aspirin, Clopidogrel, unfractionated heparin) in 8 of the 17 patients in group A and 25 of 34 patients in group B.[15] See the DHP Clinical Review by for details in the Interim Report on re-starting anticoagulant therapy.

Safety Results

Deaths

Fatal events are reported in 26 patients, 13 in each group across 123 patients: 13 deaths were reported in the 1st 5 days of the study (6 deaths in Group A, and 7 deaths in Group B). The remaining 13 deaths occurred at 6 or more days after treatment (7 in Group A

[25] BLA 761-025 Praxbind (idarucizumab), GS, Safety Update Report, p 15 of 887

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and 6 in Group B). See the DHP Clinical Review by Andrew Dmytrijuk, M. D., for details on these fatalities.[26]

A total of 11 early deaths occurred within 1 day of treatment, with 2 more deaths occurring before day 5. Early fatal events included shock with or without sepsis, peritonitis, cardiogenic shock, and circulatory collapse, progression of intracranial bleeds, multi-organ failure, cardiac arrest, ruptured aortic aneurysm and respiratory failure.

The deaths after 5 days include 8 of 26 patients. The fatal events of bleeding include circulatory collapse, shock, gastrointestinal hemorrhage (N=2), intracranial hemorrhage progression (N=3), and hemorrhagic anemia. There was only one death associated with a thrombotic event as ischemic stroke (cerebral infarction) which occurred 26 days after treatment with idarucizumab. This patient was not receiving antithrombotic therapy at the time of this event.[16]

There were 5 patients with thrombotic events during the study, 3 patients in Group A and 2 patients in Group B. Per the proposed idarucizumab substantially complete labeling, thromboembolic events were reported in 5 of 123 patients: 1 patient 2 days after treatment with idarucizumab and 4 patients, 7 days, or more after treatment with idarucizumab. None of these patients were on antithrombotic therapy at the time of the event, and in each of these cases, the thrombotic event could be attributed to the underlying medical condition of the patient. See the DHP Clinical Review for details on these 5 patient's fatalities.[16]

Adverse Events

At least one adverse event was reported for 103 of 123 treated patients (83.7%), 59 in Group A (89.4%) and 44 in Group B (77.2%). The reported events were serious adverse events (SAEs) in 53 patients (43.1%), 31 in Group A (47%) and 22 in group B (38.6%). The SAEs include fatalities as briefly cited above, immediately life-threatening, disability/incapacitation, required hospitalization, prolonged hospitalization, congenital anomaly). There were 3 patients with elevated transaminases and bilirubin who potentially met criteria for Hy's Law cases. These cases were confounded as follows: cholelithiasis with the need for urgent cholecystectomy; renal and hepatic failure and placement of a renal dialysis catheter; and sepsis, renal failure, placement of a deep vein catheter, an arterial line, and a dialysis catheter. The reported SAEs were consistent with the SAEs reported in the earlier safety data.

Hypersensitivity Reactions

There were 5 events reported to be indicative of a hypersensitivity reaction and none were causally attributed to idarucizumab. The reported adverse events in the clinical trials with idarucizumab were fever, low grade fever, bronchospasm, hyperventilation, rash, and itchiness. A causal relationship to idarucizumab could not be established (see the substantially complete proposed idarucizumab labeling, Section 6.1 Clinical Trials Experience). The risk for antibody formation to idarucizumab appears to be low and the risk for hypersensitivity reactions to idarucizumab appears to be extremely low. This comment was confirmed with the DHP Clinical Reviewer. See the DHP Clinical Review

[26] BLA 761-025 Praxbind (idarucizumab), GS, Safety Update Report, page 25 of 887

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for additional details on potential hypersensitivity reactions with idarucizumab. Per the substantially complete proposed idarucizumab labeling, Section 5.3 Warnings and Precautions, "There is insufficient clinical experience with Praxbind in patients to evaluate the risk of hypersensitivity to idarucizumab."

Immunogenicity

Sampling for anti-drug antibodies (ADA) against idarucizumab in RE-VERSE AD was planned for pre-dose (Visit 1) and one or more post-dose samples (30 ± 7 days and 90 ±7 days, Visits 5 and 6, respectively). Data are available for 47 patients with a pre-dose sample and at least one post-dose sample. There were 2 patients with baseline, non-specific ADAs both of whom had persisting ADAs at 30 days but the binding was not at the variable site. A single patient had a treatment-emergent ADA at 30 day, possibly of mixed specificity. These data are limited but appear to suggest a trend of low level of immunogenicity.[27] The DHP has raised concerns to the applicant about the assays employed for measurement of anti-dabigatran ADA.

Per the substantially complete proposed labeling (Section 6.2 Immunogenicity), using an electro-chemiluminescence based assay, serum samples from 283 patients (224 treated with idarucizumab) were tested for antibodies cross-reacting with idarucizumab. Pre-existing antibodies with cross-reactivity to idarucizumab were detected in approximately 13% (36/283) of the patients. No impact on the PK or the reversal effect of idarucizumab or hypersensitivity reactions were observed in these patients. Treatment emergent, possibly persisting anti-idarucizumab antibodies with low titers were observed in 4% (9/224) of the patients treated with idarucizumab.

Drug Interactions

Blood products such as packed red cells or fresh frozen plasma were used before and after idarucizumab treatment. A total of ~ 68% of Group A and 40% of Group B patients received blood products before or after treatment with idarucizumab. The majority of patients showed complete reversibility and there were no safety issues, it was concluded by the applicant and the Clinical Reivewer that there were no relevant drug interactions with blood products to-date.

The AEs reported from the 120-Day SUR were consistent with the clinical safety data reported from the Interim Analysis. There were no new AEs reported in the 120-Day SUR. There did not appear to be an effect of pre-existing anti-idarucizumab antibodies on the pharmacokinetics of idarucizumab in any Phase 1 study. The presence of pre-existing anti-idarucizumab antibodies did not appear to impact reversal of dabigatran-induced prolongation of clotting time for the clotting parameters, dTT and ECT.

4 DISCUSSION

Idarucizumab, a NME, is a humanized antibody fragment derived from an IgG1 isotope molecule whose target is the direct thrombin inhibitor, dabigatran. Idarucizumab is a specific reversal agent for dabigatran. The idarucizumab-dabigatran complex is characterized by a rapid on-rate and extremely slow off-rate resulting in a stable complex.

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Idarucizumab specifically binds to dabigatran and its metabolites and neutralizes their anticoagulant effect. A complete dose of idarucizumab 5 grams (two vials of 2.5 g each) is administered as an intravenous infusion (two consecutive infusions) (b) (4)

Patients being treated with dabigatran therapy have underlying disease states that predispose them to thrombotic events. Reversing the effect of dabigatran therapy exposes these patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy needs to be considered as soon as medically appropriate. Dabigatran can be initiated 24 hours after administration of idarucizumab.

The most important serious risks associated with use of idarucizumab are thrombotic events (of the patient's underlying disease) when dabigatran anticoagulant therapy is discontinued and idarucizumab reversal anticoagulant therapy is initiated and the potential risk of using idarucizumab in a patient with known hypersensitivity to idarucizumab or to any of the excipients. At this time, immunogenicity data suggests that idarucizumab has low immunogenic potential (i. e., low incidence of treatment-emergent anti-idarucizumab antibodies and low titers). The most common adverse reaction reported with use of idarucizumab is headache (12 of 224, 25% and placebo treated subjects (26/105, 25%).

The preclinical data and clinical data from volunteers in the three Phase 1 trials showed no evidence of a pro-thrombotic effect of idarucizumab. The safety of idarucizumab is well documented in these volunteers (three Phase 1 studies 1321.1, 1321.2 and 1321.5) and to-date, no dose-related adverse events or serious adverse events were reported to be causally attributed to idarucizumab.

Due to the small number of patients (26 patients) in the Phase 3 study 1321.3, interim analysis, an AE reported in one patient would be counted as having occurred in > 5% of patients in either group. Baseline morbidity in these patients treated with dabigatran in study (1321.3) make it challenging to reach a clinically meaningful conclusion at the time of this review. See **Section 3.1 Clinical Safety**, in this review for details of clinical safety data including 9 fatalities not causally attributed to idarucizumab.

The applicant submitted a RMP without a REMS proposal (b) (4) . The applicant proposes routine risk management measures including routine pharmacovigilance activities with signal detection and evaluation, periodic written reports covering ongoing clinical trials, and annual post-marketing experience. The applicant did not propose any non-REMS materials in the RMP.

The substantially complete proposed labeling does not include a Box Warning; however, it does include three potential serious risks in the Warnings and Precautions section:

- Thrombotic events that may occur secondary to the patient's underlying disease state when dabigatran is discontinued to initiate therapy with the reversal agent, idarucizumab;
- Risk of hypersensivity in patients with known hypersensitivity (e.g., anaphylactoid reaction) to idarucizumab or to any of the excipients weighed against the potential benefit of such an emergency treatment; and

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– Risk of treating a patient with Hereditary Fructose Intolerance with idarucizumab which contains 4 grams of sorbitol as an excipient in idarucizumab. Per proposed labeling, parenteral administration of sorbitol has been associated with reports of hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure with breakdown of excretory an synthetic function, (b) (4) [redacted].

Idarucizumab is a prescription only medicine, administration will be in a hospital setting with use only by trained medical personnel, for example, experienced emergency department physicians in cases where rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures, in life-threatening or uncontrolled bleeding). Other likely prescribers to use idarucizumab include surgeons, oncologists, hematologists, and internists familiar with the known risks with dabigatran including the serious risk of thrombotic events when stopping dabigatran.

Pradaxa (dabigatran) was approved on October 19, 2010 with a required REMS program consisting of a Medication Guide-only and timetable for submission of REMS assessments. The Pradaxa REMS was based on the serious risk of bleeding. Pradaxa was released from the REMS requirement on April 5, 2011. The Pradaxa labeling includes a Box Warning for: A.) Premature discontinuation of Pradaxa increases the risk of thrombotic events, and B.) Spinal/epidural hematoma. The Warnings and Precautions section includes the following risks: increased risk of thrombotic events under premature discontinuation; risk of bleeding; spinal/epidural anesthesia or puncture; thromboembolic and bleeding events in patients with prosthetic heart valves; and effects of P-glycoprotein inducers and inhibitors on dabigatran exposure.

At this time, the DRISK and the DHP concurred that idarucizumab, based on the risk of thrombotic events occurring with discontinuation of dabigatran (when initiating idarucizumab for the reversal of the anticoagulant effect of dabigatran), the risk of using idarucizumab in patients with known hypersensitivity to idarucizumab, and the risk of treating a patient with Hereditary Fructose Intolerance with idarucizumab (which contains 4 grams of sorbitol), does not need a REMS for risk management.

Post Marketing

At this time, the DHP has not communicated to the applicant on a proposed postmarketing commitment (PMC) and/or postmarketing requirement (PMR) for idarucizumab. The DHP plans to require a PMR for the applicant to complete clinical trial, study 3121.3 (case series) to further characterize safety with idarucizumab. Thrombotic events are a serious risk when reversing dabigatran therapy which exposes a patient to the thrombotic risk of their underlying disease. It is difficult to characterize clinical safety with use of idarucizumab because these patients (treated with dabigatran) have serious underlying conditions that heavily confound potential safety data. In addition, study 3121.3 is designed as a clinical trial descriptive case series without a control arm. The forthcoming safety data from completion of study 1321.3 is preferred to data from voluntary postmarketing reports because patients enrolled in study 1321.3 will be assigned to group A or B, as cited in this review.

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The applicant proposed to (b) (4)

There was discussion during the Late Cycle Meeting (July 27, 2015) with Chemistry and Manufacturing Controls (b) (4) The DHP and DMEPA are concerned about the risk of medication errors of under dosing with use of one vial (2.5 g) rather than use of two vials (each contains 2.5 g) for a total dose of 5 g. Richard Pazdur, M. D. concurred with this potential medication error risk. The applicant responded that the formulation has only been studied as two separate vials (2.5 g per vial) (b) (4)

If idarucizumab is approved, the proposed indication in patients treated with Pradaxa when rapid reversal of the anticoagulant effects of dabigatran is required (for emergency surgery/urgent procedures; in life-threatening or uncontrolled bleeding), will be under accelerated approval based on the pharmacodynamic effect of idarucizumab on dabigatran. These patients have a serious and life-threatening condition with an unmet emergency medical need in the presence of dabigatran.

5 CONCLUSION

The proposed indication in patients treated with Pradaxa (dabigatran) when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding, if approved, will be an accelerated approval based on the pharmacodynamic effect of idarucizumab on dabigatran. Per the substantially complete proposed idarucizumab labeling, (b) (4) .

At this time, based on the risks of 1) thrombotic events (of a patients underlying disease) when dabigatran therapy is discontinued and idarucizumab reversal anticoagulant treatment is initiated and 2) potential hypersensivity reactions to idarucizumab, the DRISK and the DHP concurred that a REMS is not a needed to ensure that the benefits of idarucizumab outweigh the risks for this therapeutic biologic formulation. The DHP should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for idarucizumab intravenous injection or infusion.

APPENDIX:

Table 2 Patients with AEs leading to Death

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Patient #	Age/Sex	Tx Group	SAE/death	Tx at onset	Days from Tx to Death	IDA causally related
(b) (6)	80/M	A	Parkinson's disease	Post-Tx	43	No
	83/M	A	General physical health	Post-Tx	42	No
	73/M	A	Congestive cardiac failure	Post-Tx	30	No
	60/M	A	Death	Screening	1	No
	86/F	A	Pneumonia	Post-treatment	94	No
	80/Male	B	Malignant neoplasm progression	Post-treatment	101	No
	87/Male	B	Multi-organ failure	IDA	2	No
	93/Male	B		IDA	<1	No
	87/Male	B		IDA	1	No

Abbreviations: IDA – idarucizumab; # Number; Pt - patient

Reference: BLA 761-025 Praxbind (idarucizumab), GS, Module 2.7.4 Summary of Clinical Safety, applicant's Table 2.1.5.2:1 on page 55 of 83

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/s/

CAROLYN L YANCEY
08/14/2015

CYNTHIA L LACIVITA
08/14/2015
Concur