

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761025Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

## 1 SUMMARY OF FINDINGS

### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

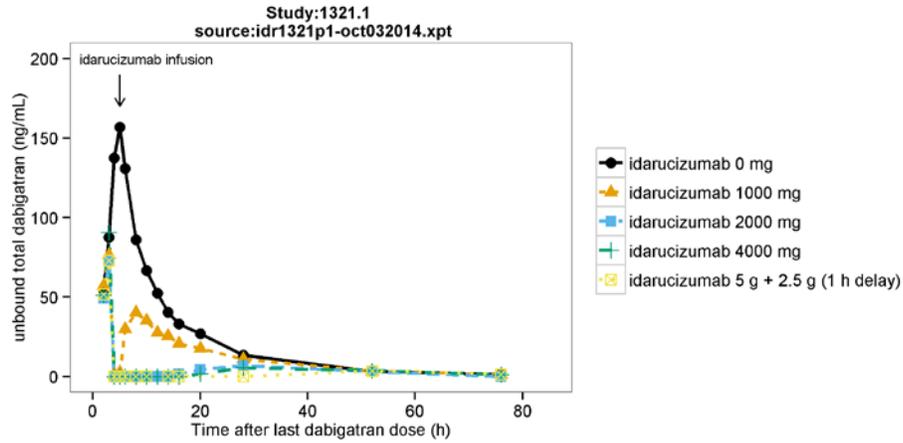
#### 1.1.1 Is the proposed idarucizumab dose (5 g) appropriate for the target population?

Yes. The appropriateness of the 5 g proposed idarucizumab dose is supported by multiple studies the applicant conducted in healthy volunteers and an open-label case series in patients. The applicant has conducted dose-finding studies in healthy male volunteers (study 1321.1). Results in **Figure 1** show that idarucizumab doses <4 g are insufficient to suppress dabigatran in healthy male volunteers. The proposed dose was subsequently tested in healthy volunteers with age and renal function status that more closely resembles atrial fibrillation patients for which dabigatran is indicated (study 1321.2). Results in **Figure 2** show that the proposed dose of 5 g is sufficient to suppress dabigatran in that population. Furthermore, dabigatran suppression in these healthy volunteer studies was achieved at concentrations that are comparable to those observed in the original dabigatran registration trials for the treatment of venous thromboembolism and the prevention of stroke in patients with atrial fibrillation (**Figure 3**).

The proposed dose of 5 g idarucizumab appears to be sufficient to suppress dabigatran concentrations in plasma and to reverse the pharmacological effect of dabigatran on blood coagulation parameters in most subjects. The following is inferred from the observed data with respect to the proposed idarucizumab dose:

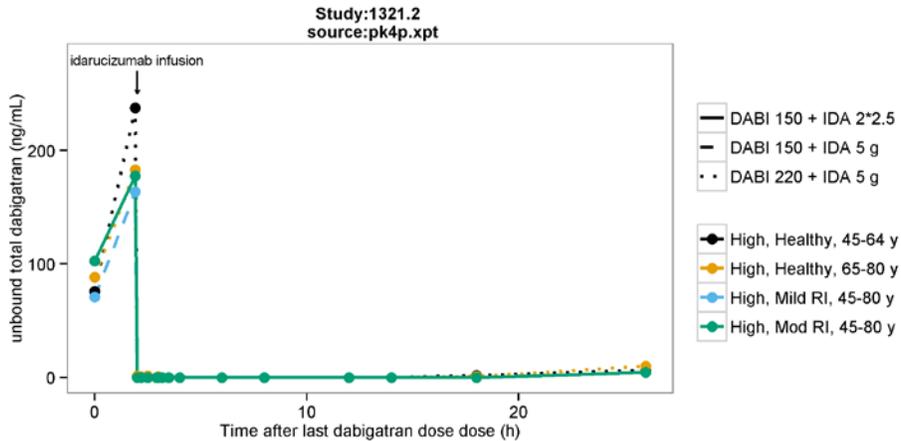
- Age (65 – 80 versus 45 – 64 years) is not a determinant of dabigatran suppression. No dose adjustment is necessary with respect to patient age.
- Renal function (mild, moderate, and normal) is not a determinant of dabigatran suppression. No dose adjustment is necessary with respect to patient renal function. However, one subject (ID 703) was observed to have high (46 mg/mL) dabigatran concentrations 26 h after the last dabigatran dose (24 h after idarucizumab infusion). The effect of renal impairment is discussed in more detail the following section **1.1.3**.
- Doses lower than 4 g are inadequate to suppress dabigatran in most subjects. To ensure best complete suppression of dabigatran the full 5 g dose should be administered to all patients.

**Figure 1: Median dabigatran concentration time profiles in healthy male volunteers following placebo or idarucizumab doses ranging from 1 to 7.5 g**



Source: dataset: idr1321p1-oct032014.xpt

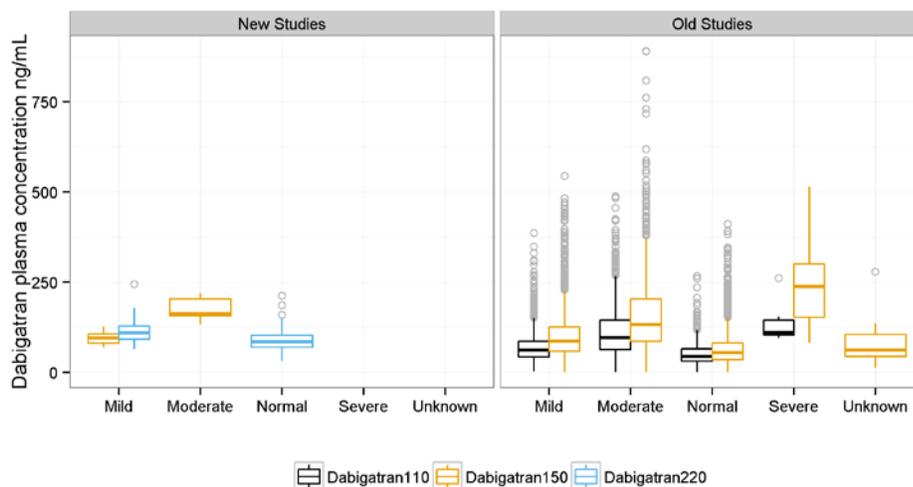
**Figure 2: Median dabigatran concentration time profiles in subjects over and under 65 years of age, with normal or impaired (mild or moderate) renal function following a 5 g idarucizumab dose**



Note: Colors indicate the study population; line type indicates the dabigatran b.i.d. dose (DABI) in milligrams and the idarucizumab dose (IDA) in grams. The IDA 2.5\*2-arm received two doses of 2.5 g idarucizumab 1 h apart. Only arms with the proposed idarucizumab dose are shown in the figure.

Source: dataset:pk4p.xpt

**Figure 3: Dabigatran steady state pre-dose sum total dabigatran exposure in the current submission (New studies) and in the dabigatran Phase 3 trials (Old studies)**



Note: Color of the box indicates the dabigatran dose, 110 mg, 150 mg, or 220 mg. Old studies: 1160.53 (treatment of venous thromboembolism), 1160.26 (prevention of stroke in patients with atrial fibrillation), New studies: 1321.1, 1321.2, 1321.5. The dabigatran concentrations here are not adjusted for protein binding.

**Table 1 Pre-Dose Concentration of Sum Total Dabigatran in Dabigatran Phase 3 Trials: 1160-0026, 1160-0053 and Idarucizumab Phase 1 Trials: 1321.1, 1321.2, 1321.5**

STUDY	REGNM	RENALGROUP	gMean	aMean	SD	Median	5th	95th	n
1160-0026	Dabigatran110	Mild	59.8	71.3	44.3	61.2	21.8	157	1582
1160-0026	Dabigatran110	Moderate	91.6	111.0	69.9	95.5	32.4	245	1297
1160-0026	Dabigatran110	Normal	43.0	51.5	32.2	43.7	15.3	111	825
1160-0026	Dabigatran110	Severe	130.0	139.0	63.5	110.0	96.4	234	6
1160-0026	Dabigatran150	Mild	84.2	101.0	62.5	88.4	27.3	212	1614
1160-0026	Dabigatran150	Moderate	129.0	158.0	99.2	133.0	46.3	351	1266
1160-0026	Dabigatran150	Normal	60.4	72.2	44.5	62.1	21.2	164	825
1160-0026	Dabigatran150	Severe	247.0	273.0	116.0	288.0	107.0	428	10
1160_0053	Dabigatran150	Mild	76.1	101.0	79.6	79.2	22.3	263	621
1160_0053	Dabigatran150	Moderate	117.0	160.0	135.0	124.0	32.0	395	248
1160_0053	Dabigatran150	Normal	47.6	63.1	52.9	49.1	12.9	167	1443
1160_0053	Dabigatran150	Severe	193.0	205.0	74.8	194.0	124.0	321	13
1160_0053	Dabigatran150	Unknown	65.9	84.0	65.3	61.3	28.0	179	15
1321.1	Dabigatran220	Mild	89.5	91.5	21.9	91.8	69.9	113	4
1321.1	Dabigatran220	Normal	73.2	76.1	20.8	74.9	43.7	109	90
1321.2	Dabigatran150	Mild	92.9	94.6	18.7	94.4	68.8	126	16
1321.2	Dabigatran150	Moderate	172.0	175.0	35.6	162.0	138.0	219	6
1321.2	Dabigatran220	Mild	113.0	118.0	35.8	111.0	77.1	169	32
1321.2	Dabigatran220	Normal	90.8	94.8	28.2	95.7	53.5	132	15
1321.5	Dabigatran220	Normal	93.9	97.1	26.5	96.0	59.2	137	96

Source: Comparison.Of.Exposures.R

### 1.1.2 What is the effect of idarucizumab administration on dabigatran exposure from the ongoing Phase 3 trial?

The recommended idarucizumab dose of 5 g is adequate to suppress dabigatran exposure in most patients. However, at high dabigatran concentrations (pre-idarucizumab administration), dabigatran levels may not be adequately suppressed. In addition, dabigatran concentration may return to levels above the limit of quantification and result in detectable anticoagulation due to redistribution of dabigatran from peripheral tissue.

Trial 1321.3 is an open label Phase 3 trial enrolling patients treated with dabigatran who have uncontrolled bleeding (Group A) or require emergency surgery or medical procedures (Group B). The reader is referred to Dr. Dmytrijuk's medical review for a review of the available data. The available preliminary data from 30 patients are shown in **Figure 4**. The following is inferred from the observed data:

- Out of 30 patients, 3 had dabigatran concentrations above 600 ng/mL. Based on applicants orientation slides from April 13, 2015, less than 1% of patients with atrial fibrillation receiving treatment with dabigatran are expected to have peak concentration of unbound total dabigatran >560 ng/mL (observations from 1160.26 [RE-LY]).
- Two patients displayed plasma dabigatran concentrations higher than observed in RE-LY Phase 3 trial.
- The 5 g idarucizumab dose was inadequate to suppress dabigatran in the patient with plasma concentrations close to 3000 ng/mL.
- The 5 g idarucizumab dose was able to initially suppress dabigatran in the patient with plasma concentrations close to 1500 ng/mL. However, due to redistribution from peripheral tissues, dabigatran concentrations returned close to 1000 ng/mL 4 h after idarucizumab administration and continued to increase up to 1500 ng/mL at 12 h after idarucizumab dose. No observations are available after 12 h in this subject.

The applicant has published an interim analysis of the ongoing Phase 3 trial<sup>1</sup> and provided an update on Trial 1321.3 as part of the 120-day safety update to the Agency. Results from both of these sources continue to support the above observations. Specifically, the publication notes:

*“The 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 (Fig. 1) and may reflect the redistribution of extravascular dabigatran into the intravascular compartment. It is uncertain*

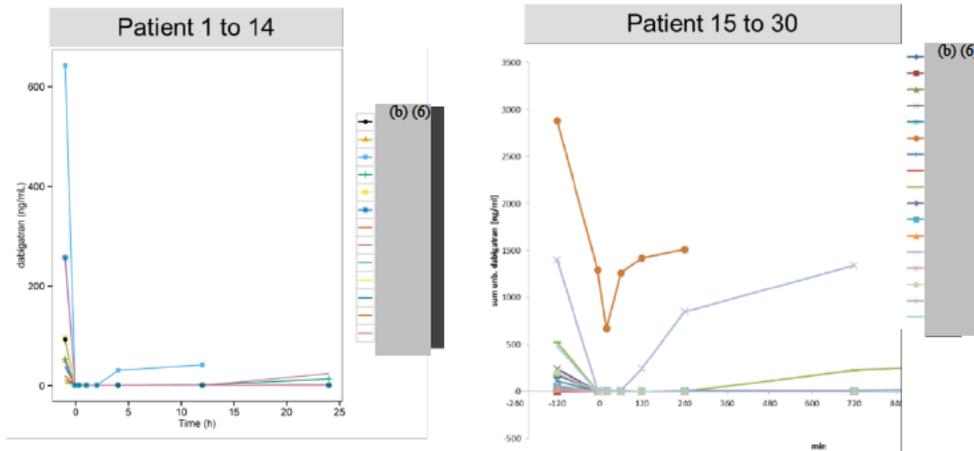
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<sup>1</sup> Pollack Jr, Charles V., et al. "Idarucizumab for dabigatran reversal." *New England Journal of Medicine* (2015).

whether patients with such a response would benefit from additional idarucizumab.”

A reviewer initiated analysis of the completed trials attempts to identify patients at risk for inadequate dabigatran suppression. Highlight from this analysis are shown in sections 1.1.3 through 1.1.5.

**Figure 4: Preliminary data from the ongoing Phase 3 trial (1321.3)**



Source: Left panel: Study report 1321.3 table 15.6.1:2 and 15.2.13:1, Right panel: adapted from Applicant's orientation slides 4/13/2015

Note: Concentration time profile for unbound total dabigatran before (Time < 0) and after (Time ≥ 0) administration of 5 g idarucizumab.

### 1.1.3 Is there a need to adjust the idarucizumab dose in patients with renal impairment?

No. Simulations conclude that subjects who have high dabigatran exposure due to renal impairment are not more likely to experience inadequate dabigatran suppression at the proposed idarucizumab dose of 5 g. No dose adjustment is needed in subjects with renal impairment.

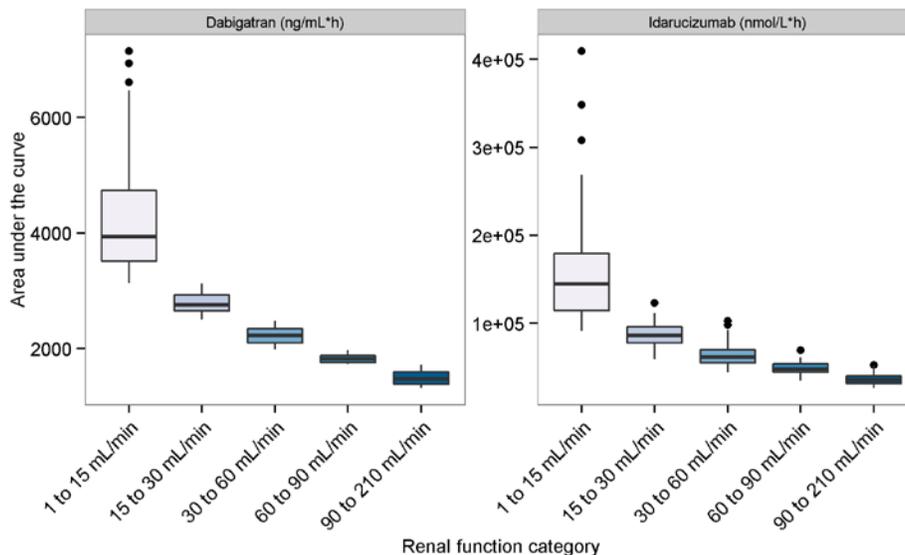
Although the applicant showed that moderate or mild renal impairment is not a determinant of dabigatran suppression in 12 subjects at the proposed idarucizumab dose, one subject was observed to have high dabigatran concentrations 24 h after the idarucizumab infusion. The reviewer has conducted clinical trial simulations using the applicant's model to investigate this issue. The following is inferred from simulations based on the applicant's model:

- Renal impairment (severe, moderate, or mild) is not a determinant of dabigatran suppression because both dabigatran and idarucizumab elimination is dependent on renal function. Both dabigatran and idarucizumab exposure will increase with decreasing renal function.

Results from stochastic simulations of dabigatran and idarucizumab exposure in patients with varying degree of renal function are shown in **Figure 5**.

The two panels in **Figure 5** show dabigatran and idarucizumab exposures when the two drugs are administered separately. The figure shows increasing dabigatran and idarucizumab exposure with decreasing renal function as measured by creatinine clearance (CRCL).

**Figure 5: Simulated Idarucizumab Area Under the Curve In Subjects With Varying Degree of Renal Function**

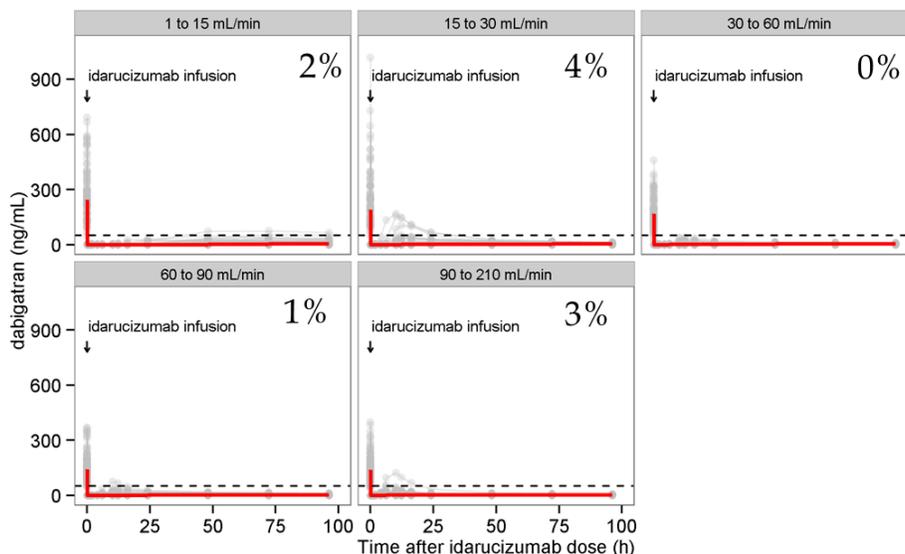


*Note: Stochastic simulations with between subject variability and residual error. Each category consists of 100 individuals.*

*Source: Simulated with model run2110.mod*

**Figure 6** illustrates simulated dabigatran exposure following idarucizumab 5 g in patients with varying degree of renal function. Some individuals are predicted to have dabigatran concentration >50 ng/mL 5 to 12 h after idarucizumab administration. This is attributed to redistribution from peripheral tissues and is consistent with the observed data. However, decreasing renal function does not increase the likelihood that appreciable redistribution will occur. The likelihood of a patient having dabigatran concentrations >50 ng/mL after idarucizumab administration ranges between 0 and 4%, with no apparent correlation to renal function. Based on these simulations the reviewer concludes that subjects who have high dabigatran exposure due to renal impairment are not more likely to experience inadequate dabigatran suppression at the proposed idarucizumab dose of 5 g.

**Figure 6: Simulated Dabigatran Concentration-Time Profile Before and After Idarucizumab Infusion In Subjects With Varying Degree of Renal Function.**



*Note:* Stochastic simulations with between subject variability and residual error. Each panel consists of 100 individuals. Idarucizumab is administered 2 h after the last dabigatran dose (150 mg b.i.d.). Individual concentrations are depicted as gray lines and circles. The median is shown by the red line. Panel headings denote range of CRCL in that patient group. The percentage of patients in each group with dabigatran concentrations > 50 ng/mL is shown in the upper right corner.

*Source:* Simulated with model run2109.mod

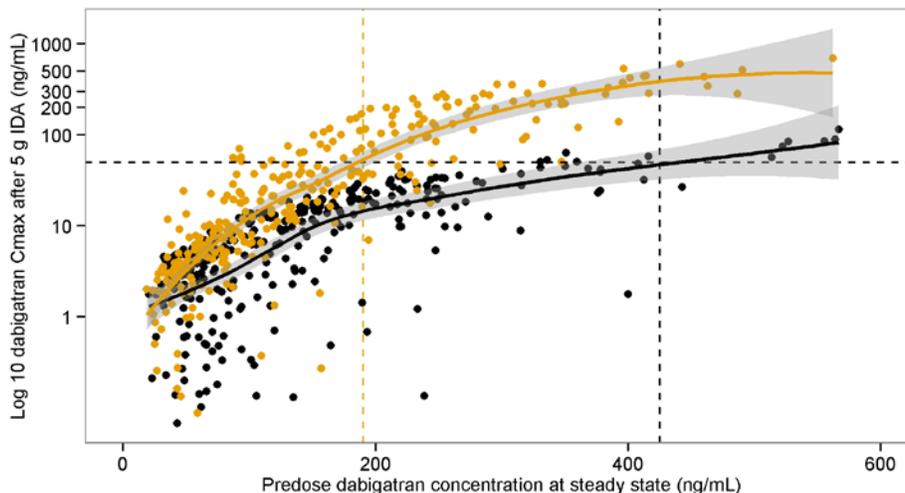
#### 1.1.4 Is there a subpopulation where the proposed dosing regimen may result in inadequate dabigatran suppression?

Yes. Steady state unbound total dabigatran trough concentrations are a predictor of inadequate dabigatran suppression. Steady-state pre-dose unbound total dabigatran concentrations > 190 ng/mL are likely to result in therapeutic dabigatran concentrations (> 50 ng/mL) 5 to 12 h after idarucizumab infusion due to redistribution from peripheral tissues if idarucizumab is administered 2 h after the last dabigatran dose. This is considered a worst-case scenario (**Figure 7**). Idarucizumab administration 12 h after the last dabigatran dose is considered a best-case scenario; give that dabigatran is administered BID. Under the best-case scenario: pre-dose unbound total dabigatran concentrations > 420 ng/mL are likely to result in therapeutic dabigatran concentrations (> 50 ng/mL) 5 to 12 h after idarucizumab infusion due to redistribution from peripheral tissues (**Figure 7**).

These findings are relevant to pre-dose concentration of dabigatran that are < 600 ng/mL. At concentrations higher than 600 ng/mL, 5 g of idarucizumab may be inadequate to suppress dabigatran or result in a dabigatran redistribution peak that occurs earlier (**Figure 4**, observed data from ongoing Phase 3 trial). This relationship does not hold if

the reason for the high dabigatran exposure is renal impairment as discussed in section 1.1.3.

**Figure 7: Simulated Steady-State Dabigatran Trough Concentrations Versus The Maximum Re-Distribution Dabigatran Concentration**



*Note:* Pre-dose steady state unbound total dabigatran trough concentrations (x axis) are plotted versus the maximum unbound total dabigatran concentration after idarucizumab infusion.

The worst-case scenario (yellow) assumes idarucizumab administration 2 h after the last dabigatran dose (at approximate  $C_{max}$ ). The best-case scenario (black) assumes idarucizumab administration 12 h after the last dabigatran dose.

The circles represent individual observations. The lines are non-parametric smoothers (loess) used for illustration purposes. The shaded area is the 95% CI around the loess line. The horizontal dashed line represents the 50 ng/mL cut off. The yellow vertical dashed line denotes the 190 ng/mL cut off for the worst-case scenario, while the black vertical dashed line denotes the 420 ng/mL cut off for the best-case scenario.

*Source:* Simulated based on models run2113.mod and run2115.mod

### 1.1.5 What is the clinical relevance of dabigatran redistribution following idarucizumab administration and what options are available to address it?

The proposed indication for idarucizumab is for patients treated with dabigatran when rapid reversal of the anticoagulant effects of dabigatran is required. Current guidelines for patients undergoing surgery recommend discontinuation of dabigatran 24 h to 5 days before the procedure, depending on renal status and risk of bleeding<sup>2</sup>. **Table 2** shows the recommendations and the predicted dabigatran plasma concentrations at the shortest recommended time. Patients with a standard bleeding risk are generally recommended to

<sup>2</sup> Van Ryn, Joanne, et al. "Dabigatran etexilate-a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity." *Thrombosis & Haemostasis* 103.6 (2010): 1116.

have dabigatran concentrations <15 to 20 ng/mL. Based on these recommendations, the elevated dabigatran concentrations due to the redistribution from peripheral tissue may also be clinically significant.

In case of emergency surgery or uncontrolled bleeding, the option to postpone the procedure until dabigatran levels have decreased to sufficiently low levels or to measure dabigatran concentration directly may not be realistic. Instead, current clinical practice guidelines recommend monitoring aPTT to determine the presence of dabigatran<sup>3</sup>. The relationship between dabigatran and the four major coagulation markers (ECT, dTT, aPTT, and TT) is shown below in **Figure 8**. Based on the available data, it may not be possible to detect dabigatran concentrations that are in range listed in **Table 2** (5-20 ng/mL) due to variability between dabigatran concentration and the coagulation markers. On the other hand, dabigatran concentrations >50 ng/mL are associated with a high likelihood of coagulation tests exceeding the upper limit of normal (ULN). Altogether, the redistribution phenomenon was deemed highly clinically significant by this reviewer if it resulted in unbound total dabigatran concentrations >50 ng/mL because:

- An unbound total dabigatran concentration >50 ng/mL is very likely to be detectable using any of the four coagulation markers. Depending on the marker, the likelihood that a coagulation marker will be above the ULN is 97.1 to 99.7%. ULN is defined as two standard deviations above the normal (mean) estimate of that biomarker from available data.
- Concentration of unbound total dabigatran at ~50 ng/mL were observed in the Phase 3 dabigatran trial) in patients with mild renal impairment administered 150 mg b.i.d. (Figure 3). As there was efficacy in this subgroup of patients in the trial it is inferred that meaningful anticoagulation occurs at these dabigatran concentrations.

It should be noted that concentrations < 50 ng/mL might be clinically significant as well. Flexibility in labeling should be afforded physicians to determine the clinical significance of elevated coagulation markers in their patient following idarucizumab administration. For example, if the option to wait until dabigatran is naturally eliminated is not viable as may be the case with emergency surgery, or if a patient is presenting with uncontrolled bleeding, labeling should permit administration of a second dose of idarucizumab based on clinical judgment. Such an approach may be particularly useful in situations when clinical signs of bleeding persist or reoccur 12 hours after the initial idarucizumab administration and anticoagulation tests confirm that coagulation markers have not returned to baseline.

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<sup>3</sup> [Cushman, Mary, et al. "Clinical Practice Guide on Antithrombotic Drug Dosing and Management of Antithrombotic Drug-Associated Bleeding Complications in Adults" February 2014](#)

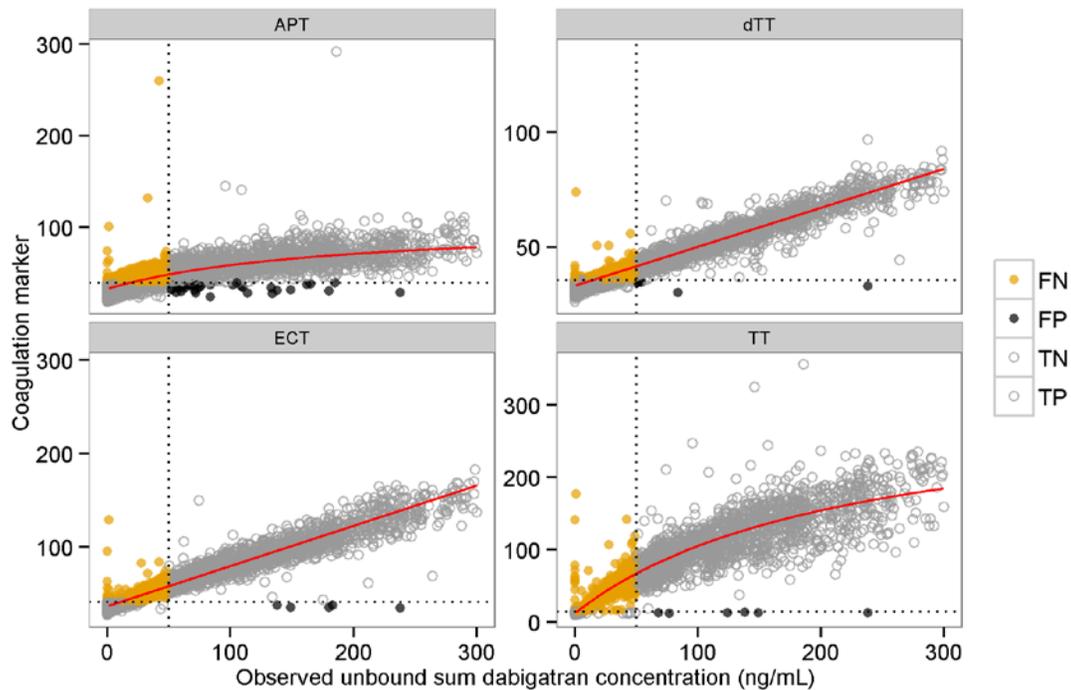
**Table 2: Guide to the discontinuation of dabigatran before elective surgery in patients with a standard or high risk of bleeding**

COPYRIGHT MATERIAL WITHHELD		<u>Estimated</u> median unbound total dabigatran plasma concentration after the shortest recommended time before surgery <sup>c</sup>	
COPYRIGHT MATERIAL WITHHELD		Standard risk of bleeding	High risk of bleeding <sup>b</sup>
COPYRIGHT MATERIAL WITHHELD		14.9 ng/mL	5.8 ng/mL
COPYRIGHT MATERIAL WITHHELD		22.9 ng/mL	9.5 ng/mL
COPYRIGHT MATERIAL WITHHELD		14.1 ng/mL	3.21 ng/mL
COPYRIGHT MATERIAL WITHHELD		10.9 ng/mL	1.84 ng/mL

<sup>c</sup> Estimated based on simulations using applicant’s population PK model (run2109 mod). CRCL clearance cut-off limits where different from those used by applicant. The cut-off values where: 90 to 210 mL/min, 60 to 90 mL/min, 30 to 60 mL/min, and 15 to 30 mL/min.

*Note: Table adapted from Van Ryn, et al. 2010<sup>2</sup>*

**Figure 8: Exposure response relationship of dabigatran and aPTT, dTT, ECT, and TT**



*Note:* Orange circles represent individual dabigatran concentration observations < 50 ng/mL that were also above the upper limit of normal (ULN) value for that coagulation marker (dotted horizontal line). These observations are considered false positive (FN).

Black circles represent individual dabigatran concentration observations > 50 ng/mL dabigatran that were also below the upper limit of normal (ULN) value for that coagulation marker. These observations are considered false negative (FP).

Gray circles represent individual dabigatran concentration observations that are on the right side of the upper limit of normal (ULN) value for that coagulation marker and the 50 ng/mL cut-off. These observations are considered to be true positive (TP) and true negative (TN).

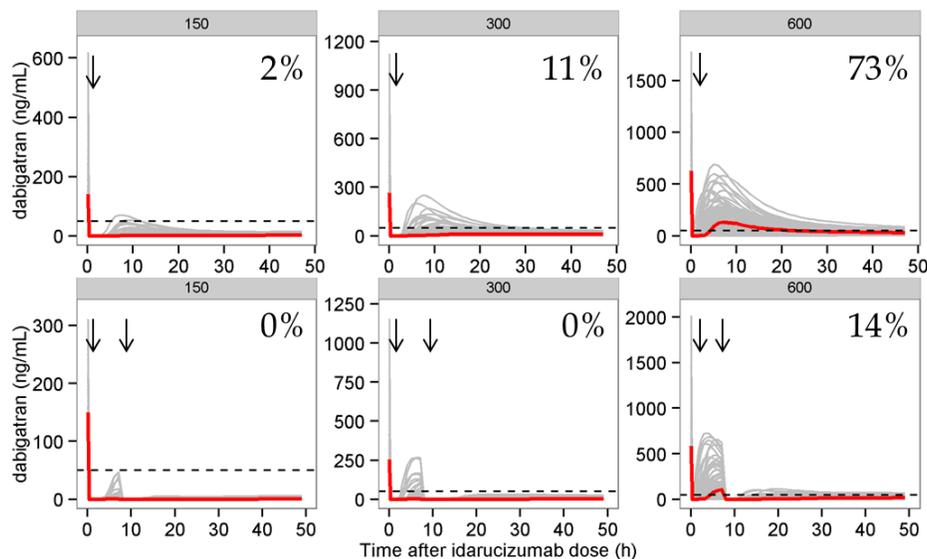
The red line represents the population exposure response relationship estimated by the applicant.

*Source:* Data: comb-ppbtsumngml-data-nov062014.xpt, model fit: applicants report, table 10.2.1, ULN values: c02742738, Appendix 16.1.9.3, Table 1.9

Simulations using the applicant’s model illustrate the effect of either one or two doses of idarucizumab on dabigatran exposure in patients at therapeutic doses of dabigatran or two and four times the therapeutic dose of dabigatran (**Figure 9**).

Upper panels of **Figure 9** show the effect of one dose of idarucizumab on 150, 300, 600 mg dabigatran b.i.d. The dashed horizontal line illustrate the 50 ng/mL cut-off and the percentages on each panel show the percent of subjects projected to have dabigatran concentrations above the cut-off after one idarucizumab dose. The lower panels illustrate the effect of two idarucizumab doses given 6 h apart.

**Figure 9: Simulated dabigatran concentration time profile following one (upper panels) or two (lower panels) doses of idarucizumab**



*Note: Each panel shows the effects of idarucizumab on dabigatran following a 150, 300, or 600 mg b.i.d. dosing regimen. Individual predictions are shown as gray lines; the red line is the median. The dashed horizontal line is the 50 ng/mL cut-off. The percentage points shows the probability of observing concentration above the cut-off following one idarucizumab dose (upper panels) or two idarucizumab doses 6 h apart (lower panels). Stochastic simulations with between subject variability and residual error. Each panel consists of 100 individuals.*

*Source: Simulated with model run2113.mod (upper panel) and run2114.mod (lower panel)*

## 1.2 Recommendations

This reviewer recommends approval provided that the Agency and the applicant can come to agreement regarding the labeling language. It is recommended that labeling include language describing that dabigatran redistribution from peripheral tissues may occur and that such redistribution can be detected using anticoagulation tests. Labeling should also permit practitioners flexibility to allow for repeat dosing of idarucizumab in cases of non-complete reversal of the effects of dabigatran (e.g., clinical symptoms of bleeding persist and anticoagulation tests indicate coagulation exceeding baseline values).

## 2 RESULTS OF SPONSOR'S ANALYSIS

The applicant has developed a model to describe dabigatran and idarucizumab disposition as well as the binding of idarucizumab and dabigatran in the studied population. Furthermore, the applicant has developed exposure-response models for dabigatran and the 4 major coagulation endpoints. Applicant's data as well as model description and model validation is reviewed in subsections below.

### 2.1 Review of Applicant's data

Three PK/PD studies have been completed in healthy volunteers and otherwise healthy subject who are above the age of 65 or have mild or moderate renal impairment. In total,

applicant has studied 14 doses of idarucizumab, ranging from 20 mg to 8 g in 220 subjects. Observations from 141 subjects are available where idarucizumab with concomitant dabigatran has been studied. Studied doses and number of subjects per trial is shown in **Table 3**.

### 2.1.1 Quantified analytes and Model-derived species

The applicant has quantified three distinct analytes, 1) unbound sum dabigatran, 2) sum dabigatran, 3) and idarucizumab. A fourth species is derived from the three measured analytes: “idarucizumab-free-sum dabigatran”, (IFSD). Applicant provides definitions for the 4 analytes in **Table 12**.

IFSD is derived in order to compare dabigatran exposure across different development programs. The following explanation is provided by the applicant:

 (b) (4)

*As a result, unbound sum dabigatran assay yields concentrations approximately 30% lower than those determined with the assay used across other earlier dabigatran programs. The population pharmacokinetic model, however, can be used to derive a concentration equivalent to sum dabigatran as quantitated in other dabigatran programs. While not necessary for characterization of the dabigatran PK/PD relationship following treatment with idarucizumab, derivation of this species allowed easier comparison of dabigatran PK and PK/PD results.”*

**Table 3: Summary of Phase I clinical trials of idarucizumab**

Study	No. of subjects	Design
1321.1	Total: N=157, males, 18-45 yrs	Randomized, double-blind, placebo-controlled, single rising dose study in healthy male volunteers
Part 1	83 treated/ 27 placebo	Single dose of 20, 60, 200, 600 mg, 1, 2, 2, 3, 4, 6, or 8 g idarucizumab as 1-h infusion or 1, 2, or 4 g as 5-min infusion
Part 2	26 treated/ 9 placebo	Single dose of 1, 2, or 4 g idarucizumab as 5-min infusion administered ~2 h after the 7th dose of dabigatran (DE 220 mg BID on Days 1-3 and QD on Day 4)
Part 3	9 treated/ 3 placebo	Idarucizumab 5 g followed 1 h later by 2.5 g, both as 5-min infusions, administered beginning ~2 h after the 7th dose of dabigatran (DE 220 mg BID on Days 1-3 and QD on Day 4)
1321.2	Total: N=46, M/F subjects	Randomized, double-blind, placebo-controlled, two-way crossover study in healthy volunteers, healthy elderly volunteers, and volunteers with mild or moderate renal impairment
Healthy	12 subjects Age: 45-64 yrs	<b>High dose</b> (N=6): Single dose of 5 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 <b>Medium dose</b> (N=6): Single dose of 2.5 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 in Period 1/2 and two months later during re-exposure on Day 4 of Period 3 <b>Dabigatran</b> : DE 220 mg BID on Days 1-3, 5, and 6 and QD on Days 4 and 7. For medium dose group only, DE 220 mg BID on Days 1-3 and QD on Day 4 of Period 3.
Healthy elderly	16 subjects Age: 65-80 yrs	<b>High dose</b> (N=8): Single dose of 5 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 <b>Low dose</b> (N=8): Single dose of 1 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 <b>Dabigatran</b> : DE 220 mg BID on Days 1-3 and QD on Day 4
Mild renal impairment	12 subjects, CrCL ≥60 to <90 mL/min Age: 45-80 yrs	<b>High dose</b> (N=6): Single dose of 5 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 <b>Low dose</b> (N=6): Single dose of 1 g idarucizumab as 5-min infusion ~2 h after the 7th dose of dabigatran on Day 4 <b>Dabigatran</b> : DE 150 mg BID on Days 1-3 and QD on Day 4
Moderate renal impairment	6 subjects, CrCL ≥30 to <60 mL/min Age: 45-80 yrs	Idarucizumab 2.5 g followed 1 h later by 2.5 g, both as 5-min infusions, administered beginning ~2 h after the 7th dose of dabigatran (DE 150 mg BID on Days 1-3 and QD on Day 4)
1321.5	Total: N=80, males, 20-45 yrs	Randomized, double-blind, placebo-controlled, sequential rising dose study in healthy Japanese male volunteers
Part 1	24 treated/ 8 placebo	Single dose of 1, 2, or 4 g idarucizumab as 5-min infusion or 8 g idarucizumab as 1-h infusion.
Part 2	36 treated/ 12 placebo	Single dose of 1, 2, or 4 g idarucizumab or 2.5 g followed 15 min later by 2.5 g, all as 5-min infusions, dosed beginning ~2 h after the dose of dabigatran on Day 11 (DE 220 mg BID on Days 1-3, QD on Day 4, BID on Days 8-10, and QD on Day 11)

BID= twice-daily; CrCL= creatinine clearance; DE= dabigatran etexilate; QD= once daily  
 Note: Subjects assigned to placebo received dabigatran but not idarucizumab in cohorts testing both drugs.  
 Source data: Clinical Trial Reports 1321.1 [c02093109], 1321.2 [c02742738], 1321.5 [c03026940]

Source: Table 8.1: 1, PopPK Report

**Table 4: Analyte definitions used for the population PK and PD analysis**

Analyte/ Model-derived species	Description
Sum dabigatran	Concentration of (bound and unbound) dabigatran in plasma plus total concentration (bound and unbound) of dabigatran metabolites (glucuronides) in plasma
Unbound sum dabigatran	Concentration of (free) dabigatran and dabigatran glucuronides not bound to plasma proteins or idarucizumab
<i>Idarucizumab-free sum dabigatran (IFSD)</i>	<i>Sum dabigatran not bound to idarucizumab</i>
Idarucizumab	Concentration of idarucizumab (free idarucizumab or idarucizumab bound to dabigatran or dabigatran metabolites)

Source: Table 8.4.1.2: 2, PopPK Report

### 2.1.2 Individual study results

The following is a summary of the idarucizumab and dabigatran interaction in the three clinical studies. Emphasis is made on the trial arms where the two products are co-administered.

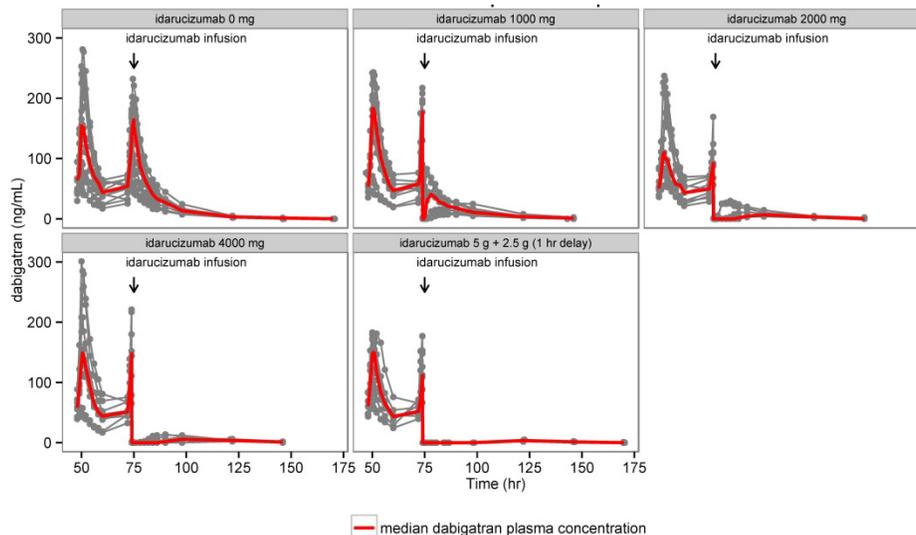
#### 2.1.2.1 Study 1321.1

Study 1321.1 was a safety and tolerability study in healthy male volunteers. Dabigatran reversal was studied using 5 different doses of idarucizumab: 1g, 2 g, 4, and 5 g + 2.5 g (separated by 1 h), and placebo (0 g). Idarucizumab and/or dabigatran administration occurred on the following days:

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2 h after Dabigatran dose)

A graphical representation of dabigatran reversal is shown in **Figure 10**. The figure displays the measured unbound total dabigatran after the first dose on day 3 and 4. Incomplete dabigatran reversal occurs following 1, 2, and 4 g of idarucizumab. The 5 g dose results in complete dabigatran reversal.

**Figure 10. Dabigatran reversal, study 1321.1**



*Note: Individual unbound total dabigatran concentrations after the first dose on days 3 and 4 are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4.*

*Source: Idr1321pl-oct32014.xpt*

### 2.1.2.2 Study 1321.5

Study 1321.5 was a safety and tolerability study in Japanese healthy male volunteers. Dabigatran reversal was studied using 5 different doses of idarucizumab: 1g, 2 g, 4, and 5 g (2.5 g\*2 separated by 15 min.), and placebo. Idarucizumab and/or dabigatran administration occurred on the following days:

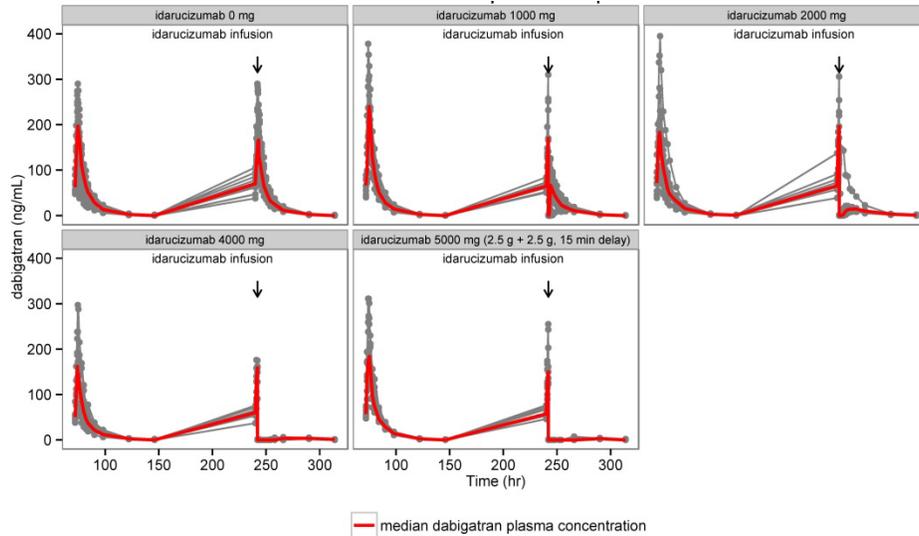
- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD)
- Day 5, 6, and 7: No drug administration
- Day 8, 9, and 10: Dabigatran (220 mg BID)
- Day 11: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2h after Dabigatran dose)

A graphical representation of dabigatran reversal is seen in **Figure 11**. The figure displays the measured unbound total dabigatran after the first dose on day 4 and 11. Incomplete dabigatran reversal occurs following 1 and 2 g of idarucizumab. Both the 4 and 5 g dose result in complete dabigatran reversal.

*Comment: Dabigatran reversal occurs at a lower idarucizumab dose in study 1321.5 compared to study 1321.1. This finding is attributed to three factors: 1) 16 % higher dabigatran CL/F in Japanese compared to others, 2) 11% lower idarucizumab CL/F in Japanese versus others, 3) overall small sample sizes from these trials that may not be*

sufficient to fully characterize the probability of incomplete reversal at the studied idarucizumab doses.

**Figure 11. Dabigatran reversal, study 1321.5**



Note: Individual unbound total dabigatran concentrations after the first dose on days 4 and 11 are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 11.

Source: Idr1321pl-oct32014.xpt

### 2.1.2.3 Study 1321.2

Study 1321.2 was a safety and tolerability study in healthy male and female volunteers, healthy elderly male and female volunteers, and male and female volunteers with mild or moderate renal impairment. Dabigatran reversal was studied using 3 different doses of idarucizumab: 1, 2.5, 5 g (as 2 2.5 g 5 min infusions separated by 15 min, or as one 5 g 15 min infusion), and placebo. Pre-dose unbound total dabigatran concentrations at steady state are shown in **Table 5**.

**Table 5. Pre-dose unbound total dabigatran concentrations at steady state**

COHORT	TREATMENT	gMean	aMean	SD	Median	Min	Max	n
High, Healthy, 45-64 y	1 DABI 220 + Placebo	69.8	72.4	19.1	74.5	39.5	93.2	6
High, Healthy, 65-80 y	1 DABI 220 + Placebo	89.4	93.9	30.4	95.8	54.9	133.0	8
High, Mild RI, 45-80 y	1 DABI 150 + Placebo	69.1	70.1	12.4	69.1	50.2	85.3	6
High, Mod RI, 45-80 y	1 DABI 150 + 2*Placebo	103.0	107.0	34.5	104.0	74.2	162.0	6
Low, Healthy, 65-80 y	1 DABI 220 + Placebo	95.2	96.2	13.7	97.8	71.1	115.0	8
Low, Mild RI, 45-80 y	1 DABI 150 + Placebo	61.7	64.0	17.0	70.2	35.8	79.0	6
Medium, Healthy, 45-64 y	1 DABI 220 + Placebo	80.4	82.8	20.4	86.4	49.3	102.0	6

Source: pk4p.xpt, Study1321.2\_plots.R

### Healthy volunteers

5 g or 2.5 g idarucizumab

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2 h. after Dabigatran dose)
- Day 5, 6, and 10: Dabigatran (220 mg BID)
- Day 7: Dabigatran (220 mg QD)

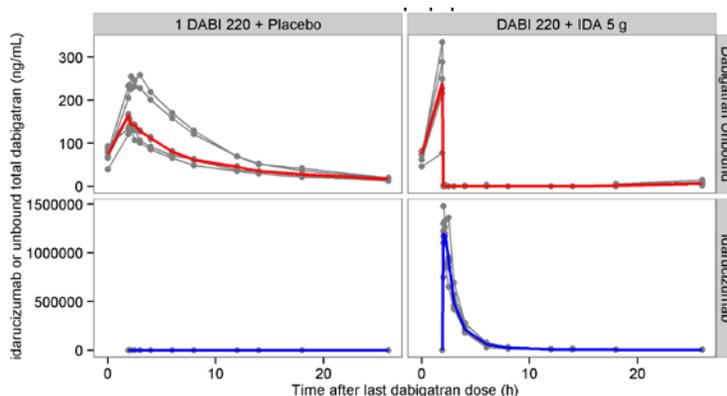
Dabigatran reversal was studied again (re-challenge) in the 2.5 g idarucizumab cohort 2 months after the first dose.

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2 h. after Dabigatran dose)

A graphical representation of dabigatran reversal is seen in **Figure 12**. The figure displays the measured unbound total dabigatran after the first dose on days 3 and 4. Incomplete dabigatran reversal occurs following the 2.5 g of idarucizumab. The 5 g dose results in almost complete dabigatran reversal in all subjects. However, dabigatran concentrations ranging from 3.08 to 15 ng/mL are observed 26 h after last dabigatran administration in all 6 subjects of that cohort. These exposures are lower than the steady state pre-dose for this cohort (median: 74 ng/mL, range: 39.5 and 93.2 ng/mL). **Figure 12 b** illustrates the reproducibility of dabigatran reversal in the same subjects at two occasions separated by two months.

**Figure 12. Dabigatran reversal, study 1321.2, Healthy volunteers**

**a)**



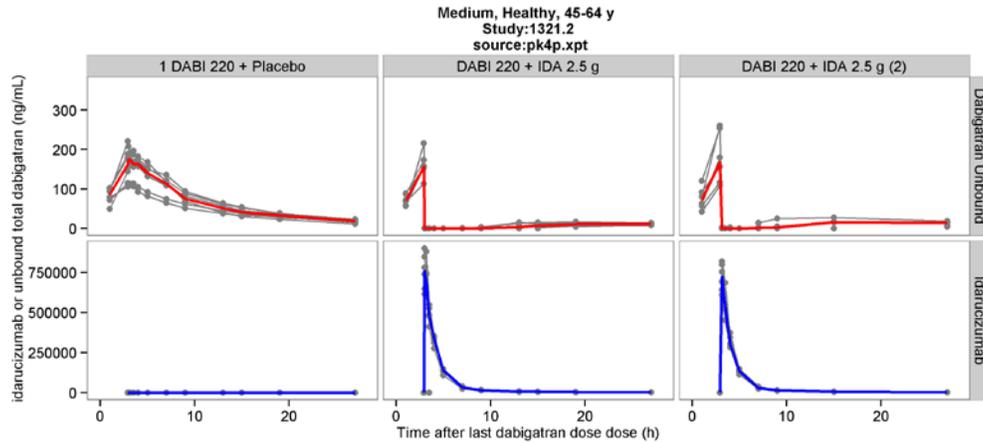
*Note:*

*Individual unbound total dabigatran concentrations after the first dose on days 3 (panel 1) and 4 (panel 2) are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4. Individual Idarucizumab concentrations on day 4 are depicted as gray lines and circles. The median idarucizumab concentration is depicted as a blue line.*

*The x-axis has been truncated to 26 h to increase clarity.*

*Source:* pk4p.xpt, Study1321.2\_plots.R

b)



Note: Individual unbound total dabigatran concentrations after the first dose on days 3 (panel 1) and 4 (panels 2 and 3) are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4. Individual idarucizumab concentrations on day 4 are depicted as gray lines and circles. The median idarucizumab concentration is depicted as a blue line.

The x-axis has been truncated to 28 h to increase clarity.

Source: *pk4p.xpt*, *Study1321.2\_plots.R*

### Healthy elderly

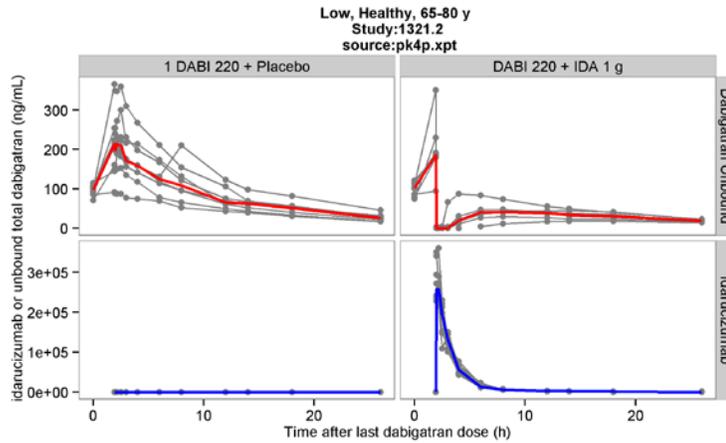
#### 5 g or 1 g idarucizumab

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2 h. after Dabigatran dose)

A graphical representation of dabigatran reversal is seen in **Figure 13**. The figure displays the measured unbound total dabigatran after the first dose on days 3 and 4. Incomplete dabigatran reversal occurs following the 1 g of idarucizumab. The 5 g dose results in almost complete dabigatran reversal in all subjects. However, dabigatran concentrations ranging from 2.32 to 15.7 ng/mL are observed 26 h. after dabigatran administration in all 8 subjects of that cohort. These exposures are lower than the steady state pre-dose for this cohort (median: 95.8 ng/mL, range: 64.4 and 133 ng/mL)

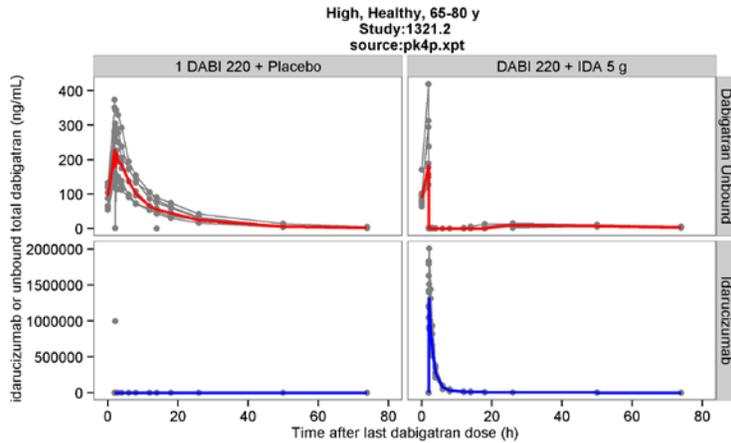
**Figure 13. Dabigatran reversal, study 1321.2, Healthy volunteers 65-80 years**

**a)**



Note: The x-axis has been truncated to 26 h to increase clarity.

**b)**



Note: Individual unbound total dabigatran concentrations after the first dose on days 3 (panel 1) and 4 (panel 2) are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4. Individual idarucizumab concentrations on day 4 are depicted as gray lines and circles. The median idarucizumab concentration is depicted as a blue line.

Source: pk4p.xpt, Study1321.2\_plots.R

**Mild renal impairment**

**5 g or 1 g idarucizumab**

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (150 mg QD) + idarucizumab (5 min infusion, 2 h. after Dabigatran dose)

A graphical representation of dabigatran reversal is seen in **Figure 14**. The figure displays the measured unbound total dabigatran after the first dose on days 3 and 4. Incomplete dabigatran reversal occurs following the 1 g of idarucizumab. The 5 g dose

results in almost complete dabigatran reversal in all subjects. However, dabigatran concentrations ranging from 6.08 to 12.4 ng/mL are observed up to 26 h. after dabigatran administration in all 6 subjects of that cohort. These exposures are lower than the steady state pre-dose for this cohort (median: 69.1 ng/mL, range: 50.2 and 85.3 ng/mL)

Moderate renal impairment

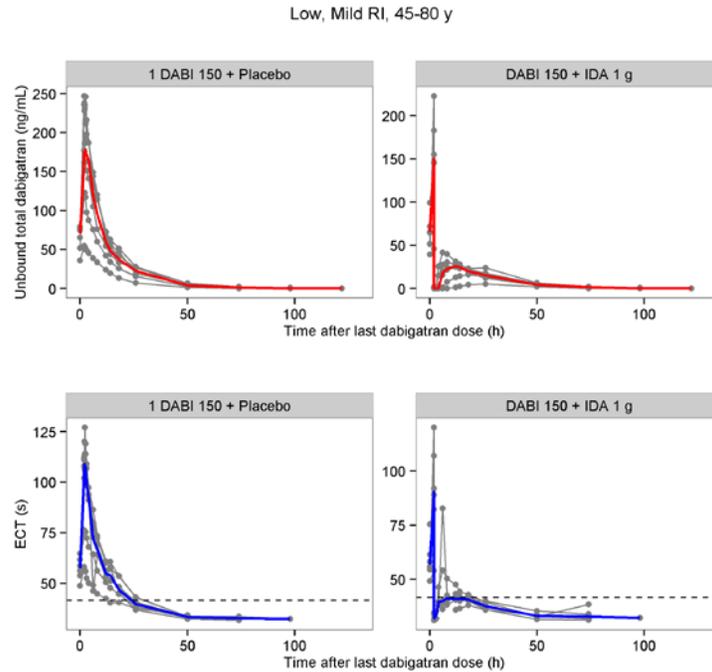
5 g idarucizumab as 2 5 min infusions of 2.5 g separated by 1 h.

- Day 1, 2, and 3: Dabigatran (220 mg BID)
- Day 4: Dabigatran (220 mg QD) + idarucizumab (5 min infusion, 2 h. after Dabigatran dose)

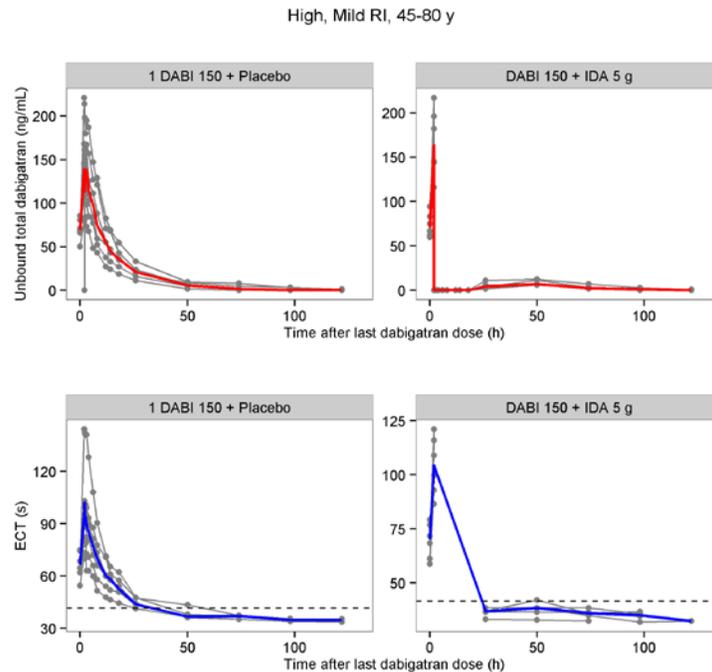
A graphical representation of dabigatran reversal is seen in **Figure 15**. The figure displays the measured unbound total dabigatran after the first dose on days 3 and 4. The 5 g dose results in almost complete dabigatran reversal in all subjects. However, dabigatran concentrations ranging from 6.52 to 18.4 ng/mL are observed up to 26 h. after dabigatran administration in all 6 subjects of that cohort. High dabigatran concentrations were observed in individual 703 at 26 h after dose (46.1 ng/mL). These exposures are lower than the steady state pre-dose for this cohort (median: 104 ng/mL, range: 74.2 and 162 ng/mL)

**Figure 14. Dabigatran reversal, study 1321.2, Subjects with mild renal impairment**

**a)**



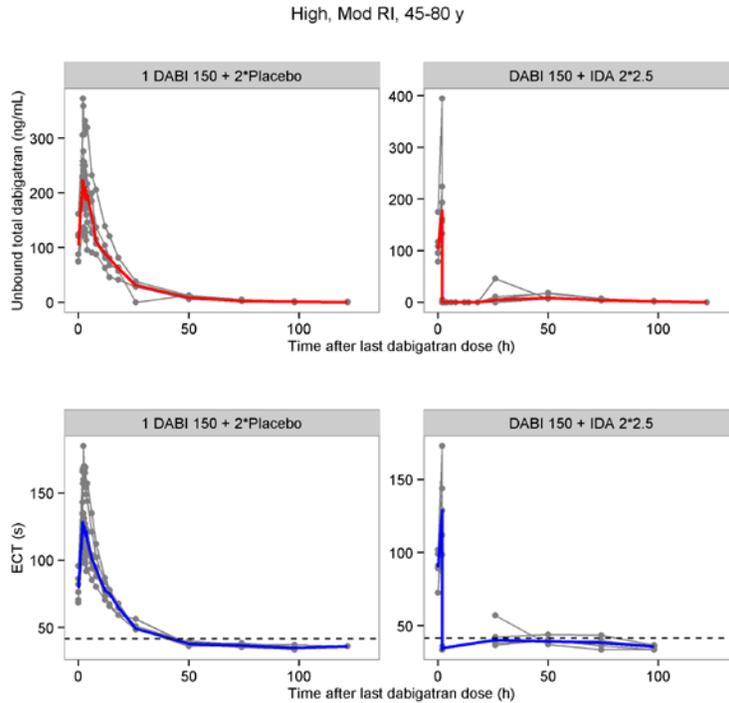
**b)**



*Note:* Individual unbound total dabigatran concentrations after the first dose on days 3 (panel 1) and 4 (panel 2) are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4. Ecarin clotting time (ECT). The median ECT is depicted as a blue line. The dashed gray line represents Mean+ 2 SD of baseline ECT (41.61 s).  
The x-axis has not been truncated

*Source:* pk4p.xpt, Study1321.2\_plots.R

**Figure 15. Dabigatran reversal, study 1321.2, Subjects with moderate renal impairment**



*Note:* Individual unbound total dabigatran concentrations after the first dose on days 3 (panel 1) and 4 (panel 2) are depicted as gray lines and dots. The red line is the observed median. Idarucizumab infusion is administered 2 h. after dabigatran administration on day 4. Ecarin clotting time (ECT). The median ECT is depicted as a blue line. The dashed gray line represents Mean + 2 SD of baseline ECT (41.61 s). The x-axis has not been truncated.

*Source:* pk4p.xpt, Study1321.2\_plots.R

## 2.2 Review of Applicants model

### 2.2.1 Idarucizumab PK model

#### Structural model

Idarucizumab disposition was described with a linear three compartment model. All fixed effect parameters were estimated with good precision RSE < 17 %. Between subjects variability (BSV) was estimated for CL, Vc and one of the peripheral volumes of distribution. These parameters were estimated with good precision, RSE < 14 %. Clearance and central volume BSV (CV%) was estimated to 11.9 and 14.8. Peripheral volume BSV was very large, estimated at 322 CV%. A full omega matrix with off diagonal elements was specified. Shrinkage was low to moderate ranging from 11-22%. The residual error was a combined additive and proportional error model. The applicant used ln-transformed data to increase model stability. Parameter estimates and their precision are tabulated in **Table 8** and **Table 9**.

### Covariate model (Idarucizumab)

Three significant covariates were found to influence Idarucizumab disposition. The effects of covariates affecting CL are illustrated in **Figure 16**.

#### CL and CRCL

Idarucizumab CL of 2.3 L/h was a function of renal clearance; when expressed as fractional CL normalized to the population prediction, the value increased from 0.69 for subjects with renal impairment (CrCL=40 mL/min) to 1.14 for healthy subjects (CrCL=120 mL/min). The covariate was estimated as a power relationship with a coefficient of 0.456

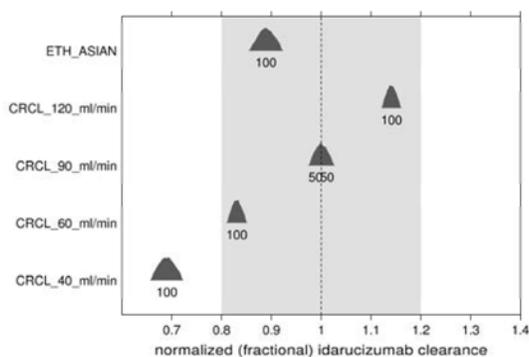
#### CL and Race

Japanese subjects were estimated to have an 11% lower clearance (e.g. factor of 0.89) compared to Caucasians/others.

#### Bodyweight and central volume of distribution (V2)

Idarucizumab central volume of distribution (3.3 L) was a function of body weight; when expressed as fractional V normalized to the population prediction, the value increased from 0.78 for a 50 kg individual to 1.34 for a 120 kg individual. The covariate was estimated as a power relationship with the a coefficient of 0.622.

**Figure 16: Plot of covariate effects on idarucizumab CL for the final idarucizumab-dabigatran binding model (run 2102)**



Source: Applicant's report, figure 10.1.4: 1.

### **Reviewer's qualification of the data and the model**

The underlying data that the model is built upon comes from a mixed population of patients with normal (182, [83%]) and impaired renal function<sup>4</sup> (38, [17 %]). The dataset included 30 elderly patients<sup>5</sup>, out of those 2 were considered very elderly. In

<sup>4</sup> Renal impairment defined as CrCL  $\geq 30$ - <90 mL/min

<sup>5</sup> Elderly defined as age  $\geq 65$  years. Very elderly defined as  $\geq 75$  years.

total 220 subjects contributed 3572 quantifiable PK samples. Selected covariates for patients that were administered idarucizumab are summarized in **Table 6**.

One major limitation of the data is the imbalance in gender and race. Only 19 female subjects and 2 Black subject were part of the final PK dataset. Due to the quality of the PK data and the diversity (with regards to renal function and age) of the population, the identified covariates are deemed credible; they do however not warrant any dose adjustments or other risk mitigation strategies. See section **1.1.3** for discussion regarding CRCL and idarucizumab dose adjustments (e.g., no idarucizumab dose adjustments are recommended based on renal function).

This reviewer has assessed the adequacy of model performance through assessment of diagnostic plots, parameter shrinkage, parameter precision, model condition number, and through simulation based diagnostics. Selected diagnostic plots are shown in **Figure 17**. Based on the above-mentioned assessments, the model is found adequate to be used in a mechanistic model describing the interplay between idarucizumab and dabigatran as well as covariate identification to account for between subject variability.

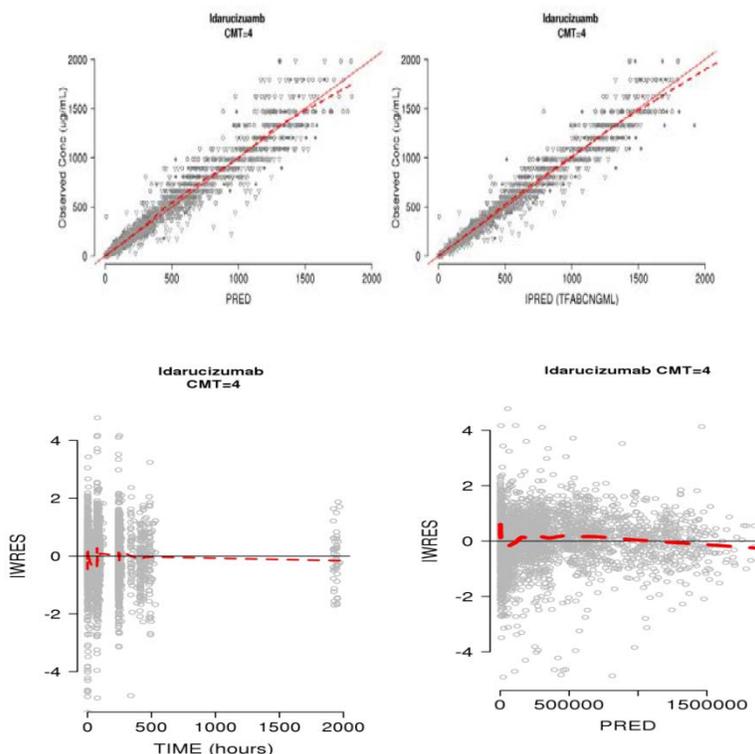
**Table 6: Selected baseline covariates for patients dosed with idarucizumab**

	Total	Study 1321.1	Study 1321.2	Study 1321.5
BW(mean)	73.7	79.3	74.2	62.6
BW(sd)	12.0	10.2	11.2	7.1
BW(min)	50	55	50	51
BW(max)	114	105	114	84
AGE(mean)	37.7	32.7	63.8	27.2
AGE(sd)	15.60	7.65	9.20	6.34
AGE(min)	20	20	45	20
AGE(max)	76	46	76	45
Elderly(n)	30	0	30	0
Very.Elderly(n)	2	0	2	0
CRCL(mean)	119.0	132.0	83.9	121.0
CRCL(sd)	28.8	23.7	20.2	19.4
CRCL(min)	44.1	79.7	44.1	89.9
CRCL(max)	213	213	157	175
Renaly.Impaired(n)	38	2	35	1
Female(n)	19	0	19	0
White(n)	158	114	44	0
Black(n)	1	0	1	0
Asian(n)	61	0	1	60
N	220	114	46	60

Note: Renal impairment defined as CrCL  $\geq 30$ -  $< 90$  mL/min  
 Elderly defined as age  $\geq 65$  years.  
 Very elderly defined as age  $\geq 75$  years. Very Elderly patients are also counted in the Elderly category.

Data source: idr1321p1-oct032014.xpt  
 Code source: Exploration\_of\_Data.R

**Figure 17: Selected Diagnostic Plots For the Idarucizumab PK Model**



Source: Applicant's report, figures 10.1.5: 1, 2, and 3.

Reviewer's comments: The diagnostic plot do not show any systematic bias as indicated by the red non-parametric smoother. There is however little difference between the PRED versus DV and the IPRED versus DV plot.

## 2.2.2 Idarucizumab-Dabigatran PK model

### Structural model

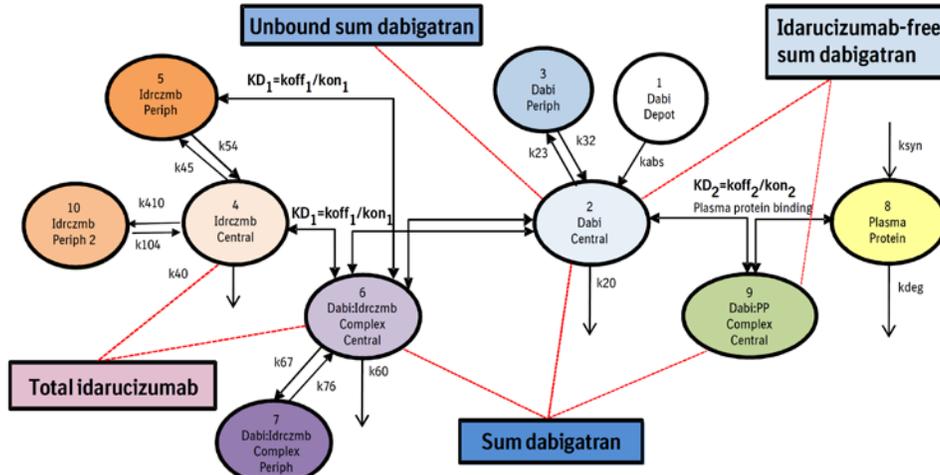
The idarucizumab component of this model is described in section 2.2.1. Dabigatran PK was best described with a two-compartment model. A protein-binding component of dabigatran was included in the model to account for the unbound and bound moiety. Absolute dabigatran bioavailability was fixed at 6.5%. Dabigatran absorption was assumed to follow a Weibull distribution, with the corresponding median absorption time ( $1/k_a$ ) of 2.54 hours (scale parameter). The shape parameter beta ( $\theta_{29}$ ) was nearly 1, at 0.96, representing near linear absorption with respect to time. Unbound dabigatran was assumed available for binding to idarucizumab in the central and one of the peripheral compartments of idarucizumab. The structural components of the model are illustrated in Figure 18. The differential equations defining the model are shown in **Table 7**. Fixed effects parameter estimates are shown in **Table 8**, random effects are shown in **Table 9**.

The applicant notes the following:

*“A notable difference between previously developed dabigatran models and the model described here is the extent of peripheral distribution. A two-compartment model developed using data from three extensively sampled Phase I dabigatran trials yielded central Vd and Vd,ss estimates of 756 L and 1101 L, respectively, for an 80 kg subject. Similar results are obtained when modeling dabigatran using data from patients not exposed to idarucizumab in the current program. However, when modeling all dabigatran data in the current program (with and without exposure to idarucizumab) central Vd and Vd,ss estimates were 278 L and 960 L, suggesting the majority of drug is distributed peripherally rather than centrally. This difference is likely influenced by simultaneous modeling of idarucizumab-mediated depletion of unbound dabigatran in the central compartment which, under the right circumstances of dose and regimen, is replaced from peripheral stores. The rate and extent of this redistribution is dependent on the amount available in the periphery, the distributional rate constants, and the relative sizes of the central and peripheral compartments. The resulting model may more accurately reflect dabigatran disposition because idarucizumab provides additional insight into the distributional kinetics of dabigatran.”*

The reviewer is inclined to agree with the applicant that the estimates of peripheral versus central distribution of dabigatran are more reliably estimated using the modeling approach based on data from dabigatran alone and concomitant idarucizumab. Therefore the previous estimates of the relative peripheral to central distribution are overestimated ( $V_c/V_{p,ss}$  0.68 versus current estimate of 0.29). The consequence of this is that less dabigatran is available for binding in the central compartment and a greater amount is protected from binding in the peripheral compartment. This reviewer believes that this is one of the reasons why profound redistribution of dabigatran from peripheral tissues is observed in some patients.

**Figure 18:** Schematic representation of dabigatran and idarucizumab PK binding model depicting a two compartment PK model for dabigatran and idarucizumab and the dabigatran:idarucizumab complex



Source: Applicant's report, figure 8.4.1.2: 1

**Table 7:** Differential equations describing the dabigatran-idarucizumab PK binding model with the complex formed from the central dabigatran and idarucizumab compartment or central dabigatran and peripheral idarucizumab compartments

(b) (4)

Source: Applicant's report, table 8.4.1.2: 1

**Table 8: Structural model (fixed effects) parameters (theta) for the final dabigatran idarucizumab model (run 2102).**

θ	Parameter	Units	EST	SE	RSE (%)	Description
1	F dabigatran	[-]	-	-	-	dabigatran bioavailability after oral administration (set to 6.5%)
2	V2/F [central] dabigatran	[L]	278	14.1	5.09	dabigatran central volume of distribution
3	V3/F [peripheral] dabigatran	[L]	682	48.6	7.13	dabigatran peripheral volume of distribution
4	Q1/F dabigatran	[L/h]	33.2	0.919	2.76	dabigatran inter-compartmental clearance
5	MAT dabigatran	[h]	2.42	0.201	8.31	dabigatran median absorption time (Weibull distribution scale parameter)
6	f <sub>u</sub> dabigatran	[%]	0.689	0.00781	1.13	fraction of dabigatran not bound to plasma proteins
7	CL/F dabigatran	[L/h]	87.2	0.798	0.915	dabigatran oral clearance
8	ALAG1 dabigatran	[h]	0	-	-	dabigatran absorption lag (fixed to 0)
9	CL idarucizumab	[L/h]	2.32	0.0319	1.38	idarucizumab clearance
10	V4 [central] idarucizumab	[L]	3.25	0.0426	1.31	idarucizumab central volume of distribution
11	V5 [peripheral 1] idarucizumab	[L]	1.96	0.335	17.1	idarucizumab peripheral volume of distribution 1
12	Q1 idarucizumab	[L/h]	0.324	0.00629	1.94	idarucizumab inter-compartmental clearance 1
13	CrCL on CL idarucizumab	[-]	0.456	0.032	7.02	power regression exponent for the relationship of individual creatinine clearance (CrCL) and idarucizumab clearance
14	BWT on V2 idarucizumab	[-]	0.622	0.0752	12.1	power regression exponent for the relationship of individual body weight (BWT) and idarucizumab central volume of distribution
15	In vivo offset for dabigatran: idarucizumab K <sub>d</sub>	[-]	0.00742	0.000379	5.11	in vivo dabigatran:idarucizumab affinity constant scaling parameter parameterized as a factor on kon
16	CrCL on CL/F dabigatran	[-]	0.341	0.0176	5.17	power regression exponent for the relationship of individual creatinine clearance (CrCL) and dabigatran oral clearance
23	AGE on dabigatran CL/F	[-]	0.059	0.00843	14.3	power regression exponent for the relationship of individual age (AGE) and dabigatran oral clearance
24	Q2 idarucizumab	[L/h]	0.272	0.00447	1.64	idarucizumab inter-compartmental clearance 2
25	V10 [peripheral 2] idarucizumab	[L]	4.03	0.0766	1.9	idarucizumab peripheral volume of distribution 2
26	COHORT 205-207 on dabigatran CL/F	[-]	0.923	0.00813	0.88	dabigatran oral clearance adjustment for renally impaired subjects (1321.2) in the presence of idarucizumab
27	COHORT 205-207 on dabigatran Q1/F	[-]	0.503	0.0223	4.44	dabigatran inter-compartmental clearance adjustment for renally impaired subjects (1321.2) in the presence of idarucizumab
28	factor race on idarucizumab CL	[-]	0.891	0.0184	2.07	Factor for race (Japanese vs. Caucasian/others) on CL idarucizumab
29	Weibull beta parameter	[-]	0.959	0.00941	0.981	dabigatran median absorption time parameter 2 (Weibull distribution shape parameter)
30	factor race on dabigatran CL/F	[-]	1.16	0.0145	1.25	Factor for race (Japanese vs. Caucasian/others) on CL dabigatran

CrCL= creatinine clearance; EST= estimate; RSE= relative standard error; SE= standard error.

Continuous covariates (CrCL, AGE, BWT) of pharmacokinetic parameters were modeled using:  $P_{TV} = \theta_1 \left( \frac{R_1}{R_{ref}} \right)^{\theta_2}$ . Categorical covariate

relationship (cohort 5-7 for study 2) was given by  $P_{TV} = \theta_1 \cdot \theta_2^{R_2}$ . P<sub>TV</sub> is a typical PK parameter,  $\theta_1$ ,  $\theta_2$ ,  $\theta_3$  are its fixed effect parameters,  $R_1$  the continuous or  $R_2$  the categorical covariate (0-1), and  $R_{ref}$  the reference value of a continuous covariate.

Source: Applicant's report, Table 10.1.4: 1

**Table 9: Variance model (between subject random effects and residual random effects) for the dabigatran-idarucizumab final model (run 2102)**

Par. #	$\omega^2$ parameter	Description	Estimate	SE	RSE (%)	IIV (% CV)
1	$\omega^2_{(1,1)}$	F1 dabigatran IIV	0.168	0.0234	13.9	42.8
2	$\omega^2_{(2,1)}$	corr F1 <sub>dabi</sub> :V2 <sub>dabi</sub>	-0.0571	0.0214	37.4	-
3	$\omega^2_{(2,2)}$	V2 dabigatran IIV	0.0914	0.0227	24.9	30.9
4	$\omega^2_{(3,1)}$	corr V3 <sub>dabi</sub> :F1 <sub>dabi</sub>	-0.131	0.0382	29.1	-
5	$\omega^2_{(3,2)}$	corr V3 <sub>dabi</sub> :V2 <sub>dabi</sub>	0.0116	0.029	24.9	-
6	$\omega^2_{(3,3)}$	V3 dabigatran IIV	0.25	0.0571	22.8	53.3
7	$\omega^2_{(4,1)}$	corr MAT <sub>dabi</sub> :F1 <sub>dabi</sub>	-0.0101	0.024	237	-
8	$\omega^2_{(4,2)}$	corr MAT <sub>dabi</sub> :V2 <sub>dabi</sub>	-0.0636	0.0193	30.4	-
9	$\omega^2_{(4,3)}$	corr MAT <sub>dabi</sub> :V3 <sub>dabi</sub>	0.0961	0.0352	36.6	-
10	$\omega^2_{(4,4)}$	MAT dabigatran IIV	0.14	0.0312	22.2	38.8
11	$\omega^2_{(5,5)}$	CL idarucizumab IIV	0.014	0.00161	11.5	11.9
12	$\omega^2_{(6,5)}$	corr CL <sub>idaru</sub> :V4 <sub>idaru</sub>	0.00698	0.00166	23.8	-
13	$\omega^2_{(6,6)}$	V4 idarucizumab IIV	0.0217	0.00308	14.2	14.8
14	$\omega^2_{(7,5)}$	corr CL <sub>idaru</sub> :V5 <sub>idaru</sub>	0.0392	0.018	45.9	-
15	$\omega^2_{(7,6)}$	corr MAT <sub>idaru</sub> :V5 <sub>idaru</sub>	0.0319	0.0238	74.6	-
16	$\omega^2_{(7,7)}$	V5 idarucizumab	2.43	0.287	11.8	322

\*all dabigatran volume and clearance terms are apparent terms

Random effects parameter estimates of inter-individual variability (IIV) are defined as %CV =  $\sqrt{e^{\omega^2} - 1} * 100\%$ . RSE% is the relative standard error (SE as % of estimate) obtained from SAEM estimation in NONMEM.

θ	Parameter	EST	SE	RSE (%)	Description <sup>1</sup>
17	residual error parameter 1 unbound sum dabigatran	0.288	0.00127	0.441	proportional component for unbound sum dabigatran
18	residual error parameter 2 unbound sum dabigatran	-0.456	0.0204	4.47	additive component for unbound sum dabigatran
19	residual error parameter 1 sum dabigatran	0.281	0.00275	0.98	proportional component for sum dabigatran
20	residual error parameter 2 sum dabigatran	-0.00507	0.00052	10.3	additive component for sum dabigatran
21	residual error parameter 1 idarucizumab	0.176	0.000834	0.474	proportional component for idarucizumab
22	residual error parameter 2 idarucizumab	0.062	0.00805	13	additive component for idarucizumab

<sup>1</sup>Combined additive and exponential error for log transformed data:  $\log(DV) = \log(f(\theta, Time)) + \sqrt{\theta_x^2 + \left(\frac{\theta_y^2}{f(\theta, Time)^2}\right)} \cdot \varepsilon_1$ , where the variance of  $\varepsilon_1$  is fixed to 1.  $\theta_x$  is the proportional component and  $\theta_y$  is the additive component of residual error with the SE on the variance scale.

Source: Applicant's report, Tables 10.1.4: 2 and 3.

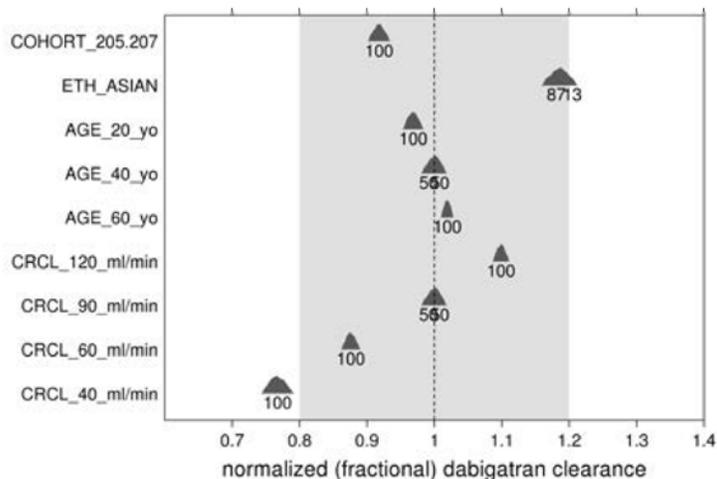
### Covariate model (dabigatran)

Previously identified covariates on dabigatran CL were confirmed in this population. The influence of CrCL, age and race dabigatran CL is shown in **Figure 19**. The typical subject dabigatran CL/F was 87 L/h, increasing as a function of renal clearance from 0.76 (66 L/h) for subjects with renal impairment (CrCL=40 mL/min) to 1.19 (104 L/h) for healthy subjects (CrCL=150 mL/min). Dabigatran clearance was 16% higher for Japanese subjects compared with Caucasian subjects.

In addition to those covariates, a cohort specific covariate was part of the final covariate model. Patients with impaired (mild to moderate) renal function were estimated to have 8% lower dabigatran CL compared to the typical reference subject in the presence of idarucizumab. Similarly, intercompartment clearance (Q/F) was estimated to be 50% lower in that cohort in presence of idarucizumab. This cohort specific covariate was used

to improve the fit of the redistribution phenomenon in these 18 subjects. Using cohort specific covariates or situation specific covariate usually indicates a knowledge gap in the understanding of the system. Although not ideal, the current approach is acceptable for the purpose of the model.

**Figure 19: Plot of covariate effects on idarucizumab CL for the final idarucizumab-dabigatran binding model (run 2102)**



Source: Applicant's report, figure 10.1.4: 1.

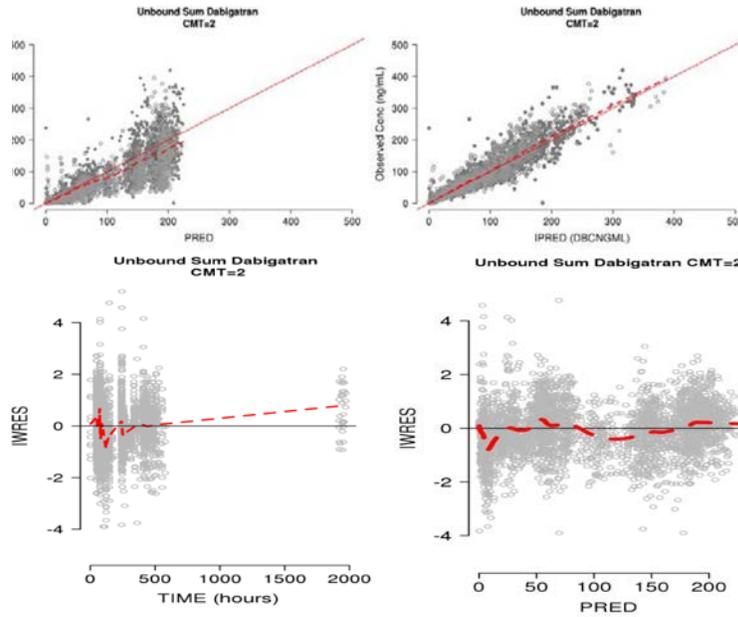
### Reviewer's qualification of the data and the model

The underlying data that the model is built upon comes from a mixed population of patients with normal (104, [74%]) and impaired renal function<sup>4</sup> (37, [26 %]). The dataset included 30 elderly patients<sup>5</sup>, out of those 2 were considered very elderly. In total 141 subjects contributed 4432 quantifiable unbound sum dabigatran PK samples. Selected covariates for patients that were administered idarucizumab are summarized in **Table 10**.

One major limitation of the data is the imbalance in gender and race. Only 19 female subjects and 1 black subject were part of the final PK dataset.

This reviewer has assessed the adequacy of model performance through assessment of diagnostic plots, parameter shrinkage, parameter precision, model condition number, and through simulation based diagnostics. Selected diagnostic plots are shown in **Figure 20**. Based on the above-mentioned assessments, the model is found adequate to be used in a mechanistic model describing the interplay between idarucizumab and dabigatran.

**Figure 20: Selected Diagnostic Plots For the Idarucizumab-Dabigatran PK model.**



Source: Applicant's report, figures 10.1.5: 1, 2, and 3.

Reviewer's comments: The diagnostic plot do not show any systematic bias as indicated by the red non-parametric smoother. There is however lite difference between the PRED versus DV and the IPRED versus DV plot.

One major limitation in these plots is that they are not stratified by concomitant administration of idarucizumab. Other revirwed diagnostic plots such as the VPC were in deed stratified and found to be acceptable for the purpose of the model.

**Table 10: Selected baseline covariates for patients dosed with dabigatran**

	Total	Study 1321.1	Study 1321.2	Study 1321.5
<i>BW(mean)</i>	71.4	78.9	74.2	61.4
<i>BW(sd)</i>	11.70	8.83	11.20	6.52
<i>BW(min)</i>	50	59	50	51
<i>BW(max)</i>	114	99	114	79
<i>AGE(mean)</i>	39.7	30.9	63.8	25.1
<i>AGE(sd)</i>	18.40	7.84	9.20	3.10
<i>AGE(min)</i>	20	20	45	20
<i>AGE(max)</i>	76	45	76	35
<i>Elderly(n)</i>	30	0	30	0
<i>Very.Elderly(n)</i>	2	0	2	0
<i>CRCL(mean)</i>	116.0	137.0	83.9	125.0
<i>CRCL(sd)</i>	31.2	25.5	20.2	18.1
<i>CRCL(min)</i>	44.1	79.7	44.1	94.7
<i>CRCL(max)</i>	213	213	157	175
<i>Renaly.Impaired(n)</i>	37	2	35	0
<i>Female(n)</i>	19	0	19	0
<i>White(n)</i>	91	47	44	0
<i>Black(n)</i>	1	0	1	0
<i>Asian(n)</i>	49	0	1	48
<i>N</i>	141	47	46	48

*Note:* Renal impairment defined as CrCL  $\geq 30$ -  $< 90$  mL/min  
Elderly defined as age  $> 65$  years.  
Very elderly defined as age  $\geq 75$  years. Very Elderly patients are also counted in the Elderly category.

*Data source:* *idr1321p1-oct032014.xpt*  
*Code source:* *Exploration\_of\_Data.R*

### 2.2.3 Idarucizumab-Dabigatran PKPD model

The applicant used linear and non-linear mixed effects modeling to describe the relationship between observed and predicted unbound sum dabigatran and four coagulation biomarkers (ECT, dTT, aPTT, and TT). The individual observed sum unbound dabigatran and the corresponding individual biomarker response as well as the population perdition of the concentration response is shown in **Figure 8**. The estimated fixed and random effects for each of the four models are shown in **Table 11**. The applicant used the exposure-response models in conjugation with the dabigatran-idarucizumab model for simulation purposes. The reviewer has evaluated the model performance of the four models and found them to be adequate for that purpose. The applicant’s simulation results are not the primary scope of this review.

**Table 11: Estimated fixed and random effects for the dabigatran-coagulation biomarker exposure-response models.**

Table 10.2.2.2: 1 Parameter estimates from the ECT final model – observed unbound sum dabigatran

Parameter	Value	RSE%	95% CI	Bootstrap 95% CI
<b>Fixed effects</b>				
Intercept [s]	36.8	0.551	36.4, 37.2	36.3, 37.2
Slope [s/ng/mL]	0.430	1.02	0.421, 0.438	0.422, 0.436
Offset_ Intercept Japanese [s] [in % of intercept]	-2.36 [-6.41]	13.6	-2.99, -1.72 [-8.13, -4.67]	-2.88, -1.78 [-7.83, -4.84]
<b>Random effects</b>				
Additive IIV on Intercept, SD	1.64	8.79*	1.38, 1.95	1.32, 1.88
Additive IIV on Slope, SD	0.0497	6.63*	0.0437, 0.0566	0.0434, 0.0549
Cov_Slope:Intercept, ρ	0.612	28.2*	0.410, 0.757	0.439, 0.829
Additive residual variability [s]	5.13	1.06*	5.02, 5.24	4.34, 5.98

\*RSE for IIV and residual variability given on SD scale; RSE for covariance term is given on the generalized logit scale.

Table 10.2.3.2: 1 Parameter estimates from the dTT final model – observed unbound sum dabigatran

Parameter	Value	RSE%	95% CI	Bootstrap 95% CI
<b>Fixed effects</b>				
Intercept [s]	31.7	0.390	31.5, 31.9	31.4, 32.0
Slope [s/ng/mL]	0.170	1.30	0.166, 0.175	0.165, 0.175
Offset_ Intercept Japanese [s] [in % of intercept]	-1.16 [-3.66]	16.8	-1.55, -0.778 [-4.89, -2.45]	-1.47, -0.815 [-4.64, -2.57]
Offset_ Intercept Pre-idarucizumab [s] [in % of intercept]	0.468 [1.48]	19.5	0.289, 0.648 [0.912, 2.04]	0.151, 0.764 [0.476, 2.41]
Offset_ Slope Japanese [s/ng/mL] [in % of slope]	0.0169 [9.94]	21.7	0.00972, 0.0241 [5.72, 14.2]	0.0106, 0.0232 [6.24, 13.6]
<b>Random effects</b>				
Additive IIV on Intercept, SD	1.06	6.92*	0.929, 1.22	0.908, 1.19
Additive IIV on Slope, SD	0.0195	6.72*	0.0171, 0.0222	0.0154, 0.0232
Additive residual variability [s]	2.23	1.07*	2.18, 2.28	1.97, 2.51

\*RSE for IIV and residual variability given on SD scale

Table 10.2.4.2: 1 Parameter estimates from the aPTT final model – observed unbound sum dabigatran

Parameter	Value	RSE%	95% CI	Bootstrap 95% CI
<b>Fixed effects</b>				
Intercept [s]	33.1	0.850	32.6, 33.7	32.5, 33.8
E <sub>max</sub> [s]	72.6	3.17	68.1, 77.1	67.1, 79.5
EC <sub>50</sub> [ng/mL]	182	4.63	166, 199	162, 205
Offset Intercept_Age [s/year] [in % of Intercept]	-0.109 [-0.329]	12.6	-0.135, -0.0818 [-0.408, -0.247]	-0.135, -0.0835 [-0.408, -0.252]
Offset E <sub>max</sub> _Japanese [s] [in % of E <sub>max</sub> ]	12.8 [17.6]	19.0	7.99, 17.5 [11.0, 24.1]	8.75, 17.5 [11.4, 22.8]
<b>Random effects</b>				
Additive IIV on Intercept, SD	2.75	7.79*	2.36, 3.20	2.25, 3.18
Additive IIV on E <sub>max</sub> , SD	12.3	8.13*	10.5, 14.4	10.2, 14.5
Cov_ Intercept:E <sub>max</sub> , ρ	0.726	37.7*	0.501, 0.859	0.519, 0.999
Additive residual variability [s]	6.84	1.07*	6.70, 6.98	4.96, 8.76

\*RSE for IIV and residual variability given on SD scale; RSE for covariance term is given on the generalized logit scale.

Table 10.2.5.2: 1 Parameter estimates from the TT final model – observed unbound sum dabigatran

Parameter	Value	RSE%	95% CI	Bootstrap 95% CI
<b>Fixed effects</b>				
Intercept [s]	12.1	1.06	11.9, 12.4	11.9, 12.6
E <sub>max</sub> [s]	301	2.59	286, 317	287, 350
EC50 [ng/mL]	223	3.44	208, 238	208, 270
Offset Intercept_WT [s/kg] [in % of Intercept]	0.0608 [0.502]	18.5	0.0388, 0.0828 [0.321, 0.684]	-0.0169, 0.134 [-0.140, 1.11]
Offset E <sub>max</sub> _Age [s/year] [in % of E <sub>max</sub> ]	-0.846 [-0.281]	20.7	-1.19, -0.502 [-0.395, -0.167]	-1.20, -0.541 [-0.399, -0.180]
Offset EC50_WT [s/ng/mL] [in % of EC50]	1.59 [0.713]	18.6	1.01, 2.18 [0.453, 0.978]	0.636, 2.53 [0.285, 1.13]
<b>Random effects</b>				
Additive IIV on E <sub>max</sub> , SD	33.5	7.75*	28.8, 39.0	0.00483, 39.9
Constant variance component, δ <sub>i</sub> #	119	47.0	47.4, 299	1.29E-07, 2861
Power variance component, δ <sub>j</sub> #	1.26	8.56	1.10, 1.43	0.505, 1.85
Remaining residual variability component, σ <sub>ij</sub>	0.0387	41.8	0.0171, 0.0880	0.00226, 1.86

\*RSE for IIV given on SD scale.

#Variance model:  $Var(\epsilon_{ij}) = \sigma^2 \cdot (\delta_i + [v_{ij}]^{\delta_j})^2$ , with  $v_{ij}$  representing observed unbound sum dabigatran concentration measurements.

Approximate variance of additive component:  $\sigma^2 \cdot (\delta_j)^2 = 21.2$  [s]

Approximate variance of power component:  $\sigma^2 \cdot (v_{ij})^{\delta_j} = 6.37\%$ CV for mean observed unbound sum dabigatran concentration (57.4 ng/mL), changing from 0.0387%CV at LLOQ to 12.8%CV at 100 ng/mL.

Notes: 95% CI of covariate effect includes 0.

Source: Applicant's tables: 10.2.2.2: 1, 10.2.3.2: 1, 10.2.4.2: 1, and 10.2.5.2: 1,

### 3 REVIEWER'S ANALYSIS

#### 3.1 Introduction

The reviewer initiated an independent analysis to investigate the dabigatran redistribution phenomenon and explore its possible causes.

#### 3.2 Objectives

Analysis objectives are:

1. Determine the cause of the redistribution phenomenon and find patient characteristics with an increased likelihood of inadequate dabigatran reversal following administration of idarucizumab 5 g.

#### 3.3 Methods

##### 3.3.1 Data Sets

Data sets used are summarized in **Table 12**.

**Table 12. Analysis Data Sets**

Study Number	Name	Link to EDR
1321.1 1321.2 1321.5	Idr1321pl-oct32014.xpt	<a href="\\cdsesub1\evsprod\bla761025\0001\m5\datasets\poppk-01-02-05\analysis\idr1321p1-oct032014.xpt">\\cdsesub1\evsprod\bla761025\0001\m5\datasets\poppk-01-02-05\analysis\idr1321p1-oct032014.xpt</a>
1321.2	pk4p.xpt	<a href="\\cdsesub1\evsprod\bla761025\0001\m5\datasets\1321-0002\analysis\pk4p.xpt">\\cdsesub1\evsprod\bla761025\0001\m5\datasets\1321-0002\analysis\pk4p.xpt</a>
1321.1 1321.2 1321.5	comb-dbcngml-data-nov062014.xpt	<a href="\\cdsesub1\evsprod\bla761025\0001\m5\datasets\poppk-01-02-05\analysis\comb-dbcngml-data-nov062014.xpt">\\cdsesub1\evsprod\bla761025\0001\m5\datasets\poppk-01-02-05\analysis\comb-dbcngml-data-nov062014.xpt</a>
1160.26	(converted from xpt) pk4p.csv	<a href="\\cdsesub1\evsprod\nda022512\0055\m5\datasets\1160-0026qc\pk4p.xpt">\\cdsesub1\evsprod\nda022512\0055\m5\datasets\1160-0026qc\pk4p.xpt</a>
1160.53	pk4pv4.xpt (user edited version of pk4pv4.xpt)  pk.csv	<a href="\\cdsesub1\evsprod\nda022512\0274\m5\datasets\1160-0053-pk-datasets\tabulations\pk4pv4.xpt">\\cdsesub1\evsprod\nda022512\0274\m5\datasets\1160-0053-pk-datasets\tabulations\pk4pv4.xpt</a>  \\cdsnas\pharmacometrics\Reviews\PM Review Archive\2014\Dabigatran_NDA22512_S018_JEL\ER Analyses\Shared Analysis Data\pk.csv

##### 3.3.2 Software

NONMEM version 7.3 was used for all the simulations. R version 3.1.1 was used for data handling, visualization, and post-processing. Piraña version 2.9.0 was used for model-handling.

### **3.3.3 Models and results**

Applicant's NONMEM control stream and their associated datasets were used for simulation of different scenarios. The applicant's NONMEM control stream was modified to facilitate simulation. MU referencing was removed. Furthermore, code that implements the M3 method for handling LOQ data was removed.

#### **3.3.3.1 Simulation of dabigatran and idarucizumab exposure (AUC) in patients with varying degree of renal function.**

Stochastic simulations with between subject variability and residual error were used to simulate dabigatran (150 mg b.i.d.) and idarucizumab (5 g single infusion) exposure in 100 subjects per renal impairment category. Patient received the two products at separate occasions in the simulations. Renal impairment was categorized by CrCL. The categories were: CrCL 1 to 15 mL/min, 15 to 30 mL/min, 30 to 60 mL/min, 60 to 90 mL/min, 90 to 120 mL/min. NONMEM control stream run2110.mod and simulation dataset Data6.csv were used for simulation. Results of the simulation are shown in **Figure 5**. Discussion in regards to the findings can be found in section **1.1.3**.

#### **3.3.3.2 Simulation of dabigatran concentration-time profile before and after idarucizumab infusion in subjects with varying degree of renal function.**

Stochastic simulations with between subject variability and residual error were used to simulate dabigatran (150 mg b.i.d.) and idarucizumab (5 g single infusion) co-administration in 100 subjects per renal function category (same as above). Patients were assumed to be on dabigatran steady state. NONMEM control stream run2109.mod and simulation dataset Data5.csv were used for simulation. Results of the simulation are shown in **Figure 6** and **Table 2**. Discussion in regards to the findings can be found in section **1.1.3**.

#### **3.3.3.3 Simulations of idarucizumab administration in patients with chronic suprathreshold dabigatran exposure that is not caused by renal impairment.**

Simulations of idarucizumab administration in patients with chronic suprathreshold dabigatran exposure, not caused by renal impairment, were conducted to find the maximum dabigatran exposure that will result in inadequate dabigatran suppression by 5 g idarucizumab. Suprathreshold dabigatran exposure was achieved by simulating dabigatran concentrations following administration of 150, 300 and 600 mg dabigatran b.i.d. NONMEM control streams run2113.mod, run2115.mod and simulation dataset Data8.1.csv and Data8.2.csv were used for simulation. Results of the simulation are shown in **Figure 7** and **Figure 9** (upper panels). Discussion in regards to the findings can be found in section **1.1.4**.

#### **3.3.3.4 Simulations of the effect of two consecutive 5 g idarucizumab doses on dabigatran concentration-time profile at therapeutic and suprathreshold dabigatran exposure.**

The effects of two consecutive doses of 5 g idarucizumab on dabigatran exposure were illustrated by stochastic simulations with BSV and residual error. The two idarucizumab doses were administered 6 hours apart. NONMEM control stream run2114.mod and

simulation dataset Data8.csv where used for simulation. Results of the simulation are shown in **Figure 9** (lower panels). Discussion in regards to the findings can be found in section **1.1.5**.

### **3.3.3.5 Summary of Results from Applicant's 120-Day Safety Update**

The applicant provided updated results on trial 1321.3 as part of the 120-day safety update submitted on June 19<sup>th</sup>, 2015. This submission included updated results on 123 patients, including 66 patients in Group A (life-threatening bleeding) and 57 patients in Group B (emergency surgery). No datasets were provided with this safety update but tabulated summaries and patient listings were included as part of the Appendices in the update. There were no bioanalytical reports provided or reviewed with the 120-day safety update but available anticoagulation (ECT, dTT, aPTT, and TT) and dabigatran measurements are summarized below as they provide additional supportive information for conclusions illustrated earlier in the review.

Of the 123 patients described in the 120-day safety update, listing of individual central lab and/or dabigatran concentration data was provided for 90 patients (51 Group A; 39 Group B; pg 804-821 of *idarucizumab-4msu-published-output.pdf*). Of these 90 patients, there were 3 patients for whom unbound sum dabigatran concentration was not available leaving 87 total patients (48 Group A; 39 Group B) with listings of both unbound sum dabigatran and anticoagulation measures. Unbound sum dabigatran and ECT at baseline for the overall set of patients and by group is shown below in **Table 13**. Median unbound sum dabigatran and ECT was 76 ng/mL and 76 s, respectively, with no discernible differences between treatment groups.

**Table 13: Unbound Sum Dabigatran and ECT by Group from Trial 1321.3**

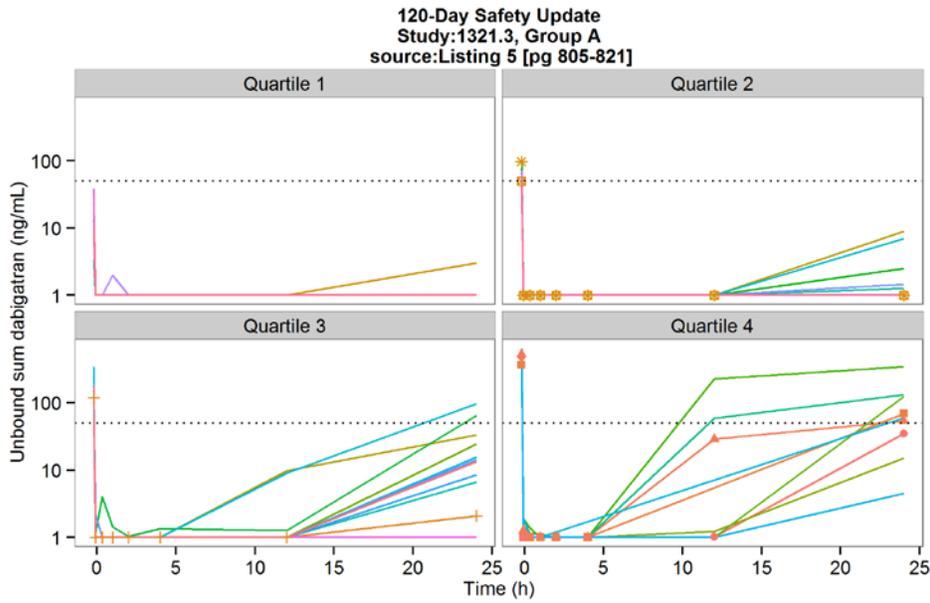
Measure	Patients	Min	25 <sup>th</sup> percentile	Median	75 <sup>th</sup> percentile	Max
Unbound Sum Dabigatran (ng/mL)	All (n=87)	3.3	38	76	195	2880
	Group A (n=48)	3.3	38	84	223	641
	Group B (n=39)	4.4	36	76	180	2880
ECT (s)	All (n=90)	35	53	76	133	500
	Group A (n=51)	37	53	78	138	315
	Group B (n=39)	35	54	74	122	500

Data source: 120-day Safety Update, Listings 5  
Code source: Safety\_Update\_Summary.R

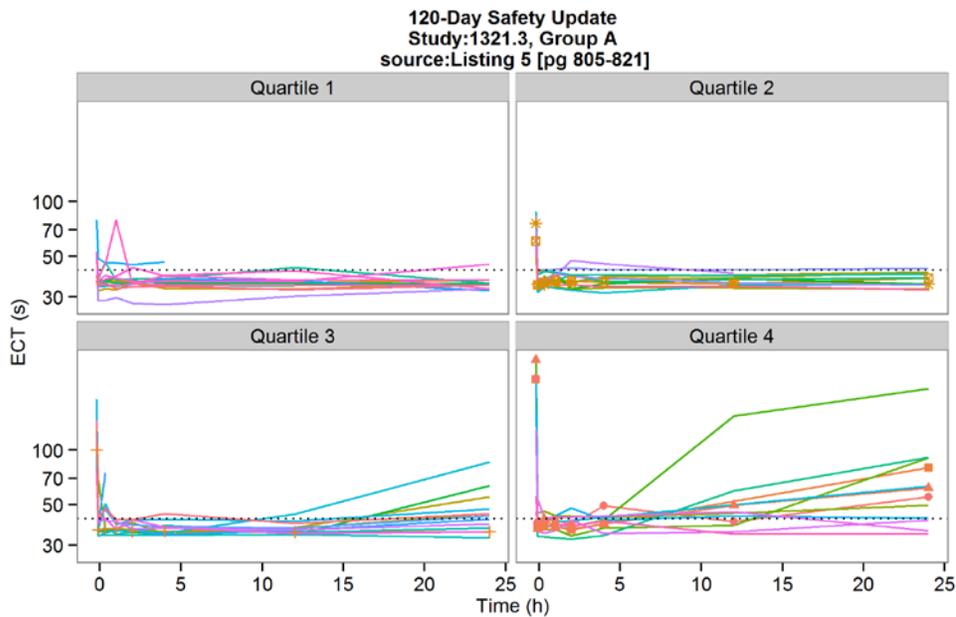
Individual unbound sum dabigatran and ECT time course profiles for all patients with listings data are shown below in **Figure 21** and **Figure 22**. Profiles are separated by treated group and further separated into quartiles by baseline sum dabigatran concentration. In all, 11 out of 87 patients (13%) had unbound sum dabigatran redistribution peaks >50 ng/mL. Patients in the highest quartile of baseline unbound sum dabigatran more commonly had redistribution peaks exceed 50 ng/mL and ECT measurements exceeding the 42 s (ULN in reviewer’s analysis). Median baseline unbound sum dabigatran in those subjects with and without post-idarucizumab redistribution peaks >50 ng/mL was 525 and 66 ng/mL, respectively. This observation is in agreement with the reviewer’s analyses in Section 1 that identifies baseline unbound sum dabigatran as a predictive factor for occurrence of unbound sum redistribution peaks >50 ng/mL.

**Figure 21: Unbound sum dabigatran (a) and ECT (b) time course profiles for Group A patients from trial 1321.3 (120-day safety update). Patients are further grouped according to baseline unbound sum dabigatran quartile.**

a)



b)



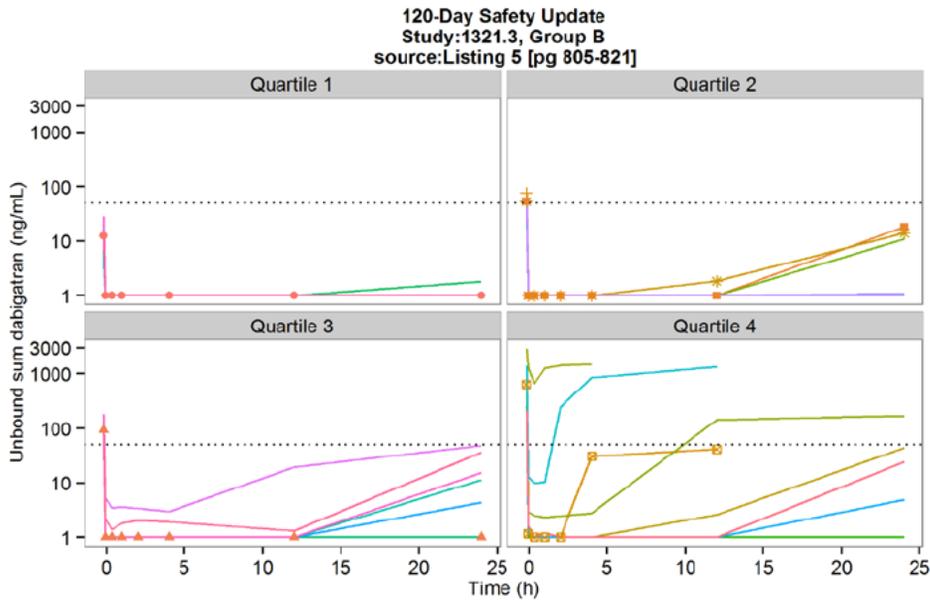
Source: 120-day safety update, Listing 5, Group A data

Note: Concentration and ECT time profile for unbound total dabigatran before (Time < 0) and after (Time ≥ 0)

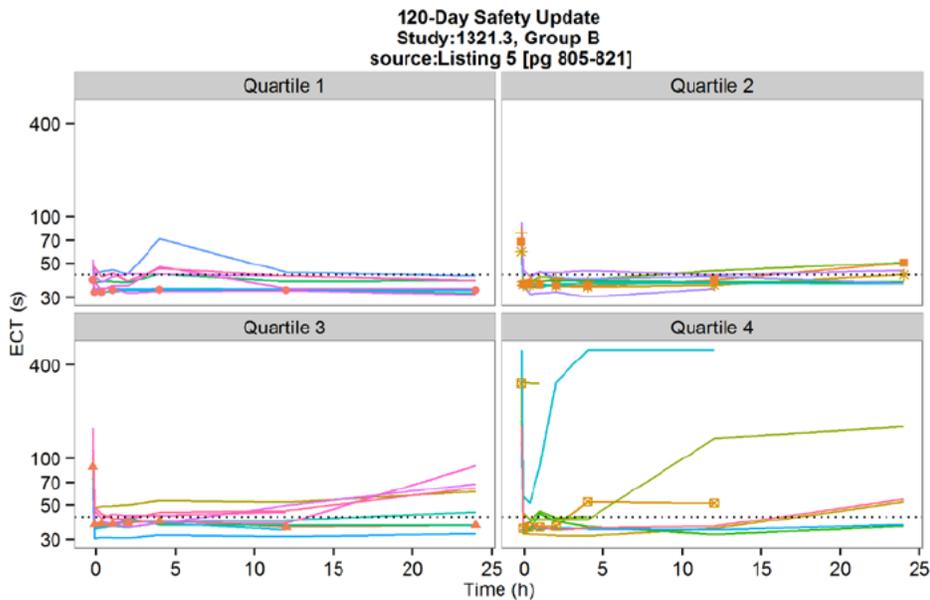
administration of 5 g idarucizumab. Horizontal lines depict: a) 50 ng/mL and b) 42 s (ULN).

**Figure 22: Unbound sum dabigatran (a) and ECT (b) time course profiles for Group B patients from trial 1321.3 (120-day safety update). Patients are further grouped according to baseline unbound sum dabigatran quartile.**

a)



b)



Source: 120-day safety update, Listing 5, Group B data

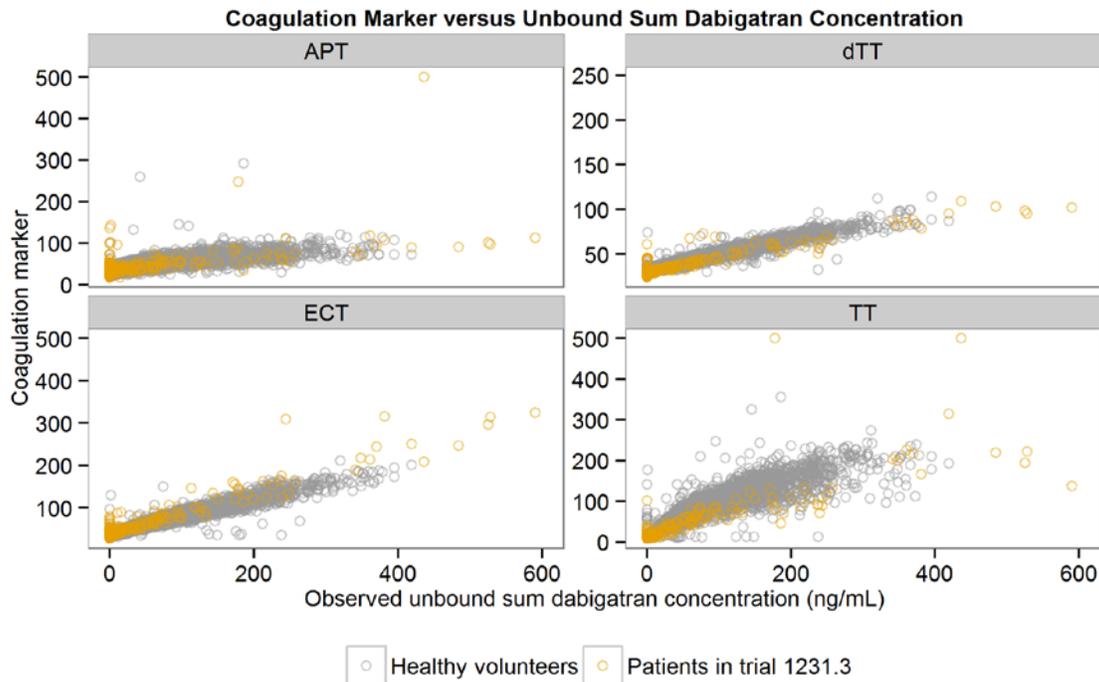
Note: Concentration and ECT time profile for unbound total dabigatran before (Time < 0) and after (Time ≥ 0)

administration of 5 g idarucizumab. Horizontal lines depict: a) 50 ng/mL and b) 42 s (ULN).

Finally, a comparison between dabigatran concentration and the four major coagulation markers (ECT, dTT, aPTT, and TT) from healthy volunteers (1321.1 and 1321.2) and patients in trial 1321.3 is shown below in Figure 23. It is recognized that the patient population may have additional ongoing interventions compared to healthy volunteers, but the available data supports that the dabigatran~coagulation marker relationships are unchanged between these groups. This observation supports that:

- Inferences drawn from the dabigatran~coagulation relationships in healthy volunteers are applicable to the patient population
- Post-idarucizumab increases in ECT, dTT, aPTT, and TT, assessed in the target patient population, reflects redistribution of dabigatran from peripheral tissue

**Figure 23: Exposure response relationship of dabigatran and aPTT, dTT, ECT, and TT for healthy volunteers and patients from trial 1321.3**



*Note:* Orange circles represent individual dabigatran concentration observations < 50 ng/mL that were also above the upper limit of normal (ULN) value for that coagulation marker (dotted horizontal line). These observations are considered false positive (FN).

*Source:* Data: comb-ppbtsumngml-data-nov062014.xpt, model fit: applicants report, table 10.2.1, ULN values: c02742738, Appendix 16.1.9.3, Table 1.9, 120-day safety update, Listings 5

#### 4 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Data6.csv	Data for run2110.mod. Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
Data8.csv	Data for run2114.mod. Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
Data8.1.csv	Data for run2113.mod. Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
Data8.2.csv	Data for run2114.mod. Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
Data5.csv	Data for run2109.mod. Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
run2110 mod	Model to generate <b>Figure 5</b> . Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
run2113 mod	Model to generate <b>Figure 9</b> . Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
run2115 mod	Model to generate <b>Figure 9</b> . Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses
run2109 mod	Model to generate <b>Figure 6</b> and <b>Table 2</b> Created by Simulations.R	Idarucizumab_BLA761025_DR\PPK Analyses

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/s/  
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DINKO REKIC  
09/15/2015

JEFFRY FLORIAN  
09/15/2015

## CLINICAL PHARMACOLOGY REVIEW

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Proposed Brand Name	Praxbind
INN Name	Idarucizumab
BLA Number and Type	761,025
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Submission Date	2/19/2015
Proposed Indication	Rapid reversal of the anticoagulant activity of dabigatran for (1) emergency surgery/urgent procedures, and (2) life-threatening or uncontrolled bleeding
Dosage Form & Strengths	Solution for injection/infusion 2.5 g/50 mL (50 mg/mL) per vial
OCP Division	DCP I and DPM, Cardiovascular and Renal Products Team
OND Division	OHOP, Division of Hematology Products
Reviewer	Martina Sahre, PhD Dinko Rekić, PhD
Team Leader	Rajanikanth Madabushi, PhD Jeffrey Florian, PhD

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### 1 Executive Summary

#### 1.1 Recommendations

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. Based on the review, OCP has the following additional labeling recommendation (see Question 2.2.4.4 for details):

The labeling 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. If such elevations in coagulation parameters are associated with reappearance of clinically relevant bleeding, an option for re-dosing idarucizumab (5g) in those patients should be provided in the label.

#### 1.2 Recommended Phase 4 Study Commitments

None.

#### 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Idarucizumab is a humanized antibody fragment (Fab) developed to bind dabigatran in plasma, and in this manner reverse dabigatran's effect on coagulation.

The Clinical Pharmacology program includes studies that characterize the pharmacokinetics of idarucizumab, the effect on dabigatran pharmacokinetics and clinical coagulation markers

in three Phase 1 PK/PD studies. Preliminary data from an ongoing open label observational Phase 3 study are also available.

The following are the salient findings of the review:

### **Idarucizumab pharmacokinetics**

- 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.
- Idarucizumab, as an antibody fragment, is likely metabolized by proteases in vivo, and excreted renally. Renal excretion of idarucizumab ranged from 8 to 40% in the range from 1 to 8 g, pooled over available studies. This may be due to saturable catabolism or tubular reabsorption in the kidney.
- 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 goes 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.

### **Idarucizumab Pharmacodynamics**

- 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 around ~24 hours following idarucizumab administration. One subject had a distribution peak of 46 ng/mL.

- Redistribution resulting in dabigatran exposures exceeding 50 ng/mL, a detectability threshold that represents dabigatran-induced anticoagulant activity, is likely to occur in subjects with pre-dose unbound sum dabigatran concentrations above 190 ng/mL. Based on data from the RE-LY, redistribution of this magnitude may occur in at least 10% of patients receiving dabigatran 150 mg BID.
- For patients with very high initial dabigatran concentrations (>600 ng/mL, unbound sum), 5 g of idarucizumab is unlikely to suppress the effects of dabigatran. Three (out of 30) patients were observed to have dabigatran concentrations at these high levels in the on-going open label Phase 3 study. Anticoagulation due to dabigatran was not completely reversed in these subjects.
- Repeat administration two months after initial treatment with idarucizumab showed similar suppression of unbound sum dabigatran exposures with a corresponding reversal of dabigatran-induced anticoagulant activity.
- 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.

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Definition of key terms used throughout the document

Parameter	Definition
Sum Dabigatran	Concentration of dabigatran and dabigatran glucuronide combined, measured after glucuronide hydrolysis
Unbound sum dabigatran	Sum dabigatran concentrations that are not protein bound, <div style="background-color: #cccccc; padding: 2px; display: inline-block;">(b) (4)</div>

## 2 Question-Based Review

### 2.1 General attributes of the drug

Idarucizumab was developed as a dabigatran reversal agent. Dabigatran is a direct thrombin inhibitor, used to (1) reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillations, (2) treat deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days, and (3) to reduce the risk of recurrence of DVT and PE.

So far, there is no reversal agent to dabigatran available on the market.

During development, the applicant interacted with the Agency on multiple occasions, specifically on the matter of studies needed to show reversal of dabigatran anticoagulation. Idarucizumab acts by binding dabigatran, mostly in the vasculature, and thereby potentially returning the system to a state where no direct thrombin inhibition is present. Therefore, studies showing that idarucizumab can return clinically used clotting parameters to a baseline state was thought to constitute evidence of effectiveness. This could be demonstrated in pharmacokinetics/pharmacodynamic studies (PK/PD) in healthy subjects as well as patients with renal impairment, as it is known that they represent a population at risk of increased dabigatran exposure.

The clinical pharmacology of dabigatran has been extensively reviewed in its original and subsequent submissions. The reader is referred to these reviews<sup>1</sup> (DARRTS NDA 22,512, review by Krudys (8/24/2010), Mishina (9/8/2010 and 11/30/2010), Hinderling (1/31/2011, 2/3/2011, 11/18/2011, and 8/23/2012), Madabushi (2/19/2011), Hariharan (4/25/2012 and 8/7/2014), Bullock (3/7/2014), Lee (3/7/2014 and 3/12/2014), Zineh (3/7/2014), and Moon (3/10/2014 and 11/19/2014)).

2.1.1 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Idarucizumab is a humanized Fab fragment directed against dabigatran and is derived from a murine IgG1 antibody. The molecular mass of idarucizumab is approximately 47,766 Da.

The drug product is a clear to slightly opalescent solution for injection or infusion containing 50 mg/mL idarucizumab in a 50 mL vial as well as acetic glacial acid and sodium acetate trihydrate (b) (4), polysorbate 20 (b) (4), sorbitol (b) (4), and water for injection.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Dabigatran binds to idarucizumab (Figure 1) with more than 300 times greater affinity than the binding of dabigatran to thrombin. By binding dabigatran that would otherwise bind to thrombin, the anticoagulant effect of dabigatran is reversed.

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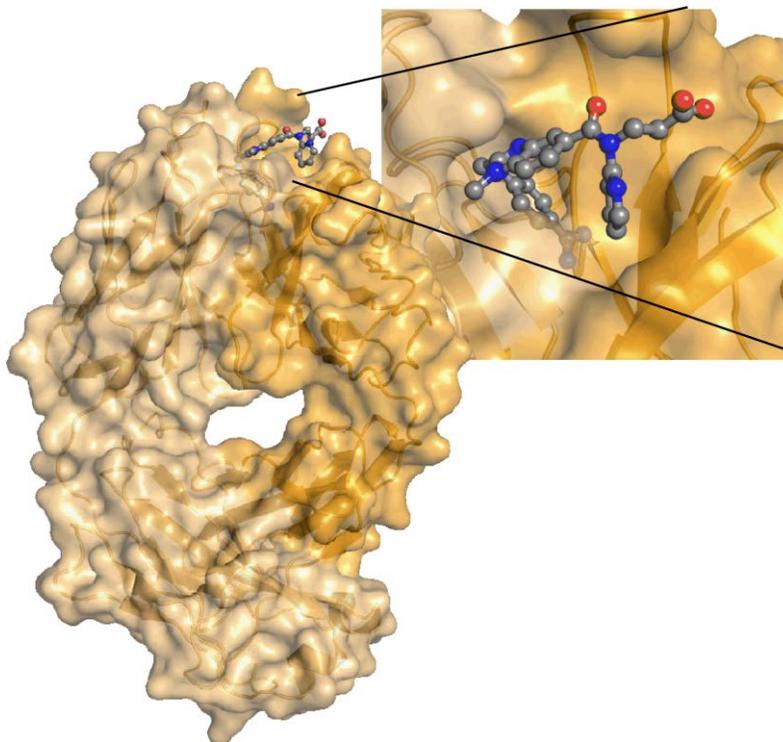
<sup>1</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2010/022512Orig1s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000TOC.cfm)

In vitro studies indicate that dabigatran binds to idarucizumab with high affinity ( $K_D$  on average 2.1 pM). The association ( $k_a$ ) and dissociation ( $k_d$ ) rate constants are  $3.4 * 10^5 M^{-1}s^{-1}$  and  $0.7 * 10^{-6}s^{-1}$ , respectively. The estimated half-life of the complex is 260 h, which implies that the binding is effectively permanent for the duration of residence of these molecules in the body. Binding affinities are slightly affected by pH, where the average  $K_D$  ranges from 9 pM at a pH of 6.7 to 1 pM at a pH of 8.0. This, however, is still larger than the binding affinity of dabigatran for thrombin ( $K_D = 0.7$  nM or 700 pM) and is not expected to change the effect of idarucizumab.

Idarucizumab did not show affinity for various thrombin substrates *in vitro* (including Factors V, VIII, XIII, von Willebrand factor, and protein C). Idarucizumab did not show prothrombotic activity in a thrombin generation assay, in an ecarin thrombogenic assay, and a rat tail model.

The indications sought are for the rapid reversal of dabigatran action in patients who are taking dabigatran and (1) need emergency surgery or urgent procedures, or (2) have life-threatening or uncontrolled bleeds.

**Figure 1. Dabigatran binding to idarucizumab (x-ray crystallography representation)**



Source: Applicant's Non-clinical Summary Pharmacology; Section 2.6

### 2.1.3 What is the proposed dosage regimen and route of administration?

The proposed dose is 5 g idarucizumab given (2 vials containing 2.5 g each) as two consecutive infusions [REDACTED] (b) (4) or as a bolus injection. The solution should be administered within an hour of being removed from the vial.

The product should not be administered in the same intravenous line with other medicinal products at the same time. If a pre-existing i.v. line is used for administration, it should be flushed with normal saline prior to use.

## 2.2 General clinical pharmacology

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The applicant conducted three Phase 1 PK and PD studies (Table 1).

The applicant is also conducting a Phase 3 open-label, observational study in patients receiving idarucizumab for the reversal of dabigatran in life-threatening or uncontrolled bleeding, and in patients who need reversal of dabigatran for emergency surgery/procedures. This study (1321.3, REVERSE-AD) is currently ongoing and will enroll approximately 200 to 300 patients.

**Table 1. Listing of Clinical Pharmacology Studies**

Study	Population, N	Doses	Type
1321.1	Healthy male subjects; N=157	20 mg to 8 g idarucizumab with and without 220 mg BID dabigatran	First-in-human
1321.2	Healthy subjects 45-60 and 60-80 y, and subjects with mild and moderate renal impairment (45-80 y); N=46	1 to 5 g idarucizumab, with and without 220 (150) mg BID dabigatran Re-dosing with dabigatran Re-dosing with idarucizumab 2 months after the first treatment	Dose selection, specific populations
1321.5	Healthy, male Japanese; N=80	1, 2, 4, 8 g idarucizumab or placebo With and without dabigatran 220 mg BID	Safety, tolerability and PK, PD

### 2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The endpoints in the Phase 1 PK/PD evaluations are clinically used markers of the clotting cascade, all of which demonstrate a strong correlation with dabigatran exposure. These include activated partial thromboplastin time (aPTT), thrombin time (TT), ecarin clotting time

(ECT), and diluted thrombin time (dTT, not approved in the United States), and activated clotting time (ACT). Current guidelines<sup>2</sup> suggest using charcoal if the dabigatran ingestion occurred less than 2 h previous, followed by measurement of aPTT. If aPTT is prolonged, treatment includes volume resuscitation and hemodynamic support, as well as transfusion and elucidation of the bleeding source.

2.2.3 Are the active moieties in plasma and urine appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Idarucizumab and dabigatran were identified and quantified in plasma and urine using methods that were successfully validated prior to use and that fulfilled pre-specified acceptance criteria throughout study sample analysis. Refer to section 2.6 for details about the analytical methods.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Exposure-response analyses for this submission focus on the binding of idarucizumab to dabigatran and subsequent elimination of the bound complex from systemic circulation resulting in reversal of the anticoagulant activity of dabigatran. While these are not direct outcome measures, they reflect the mechanism of action of idarucizumab and the underlying clinical situation (i.e., an anticoagulated state due to dabigatran exposure that results in life-threatening or uncontrolled bleeding or a need for rapid reversal in the event of emergency surgery or urgent procedures)

Idarucizumab suppressed unbound sum dabigatran concentrations (Figure 2, top), and consequently restore coagulation to baseline levels (20-30 s) based on ECT, the primary pharmacodynamic measure (Figure 2, bottom). Similar reversal in dabigatran-induced anticoagulation based on other coagulation markers, such as aPTT, TT, dTT and ACT, was also observed. Dabigatran suppression begins immediately upon administration of idarucizumab, though the offset characteristics are ultimately dependent on the amount of idarucizumab administered and steady state levels of dabigatran. This issue is explored in further detail below and in subsequent questions

The duration of suppression of unbound sum dabigatran concentrations was dose dependent. An idarucizumab dose of 1 g was sufficient to suppress dabigatran exposures for only a short period of time. A more sustained suppression is observed with the 7.5 g dose compared to doses of 1 g, 2 g, or 4 g.

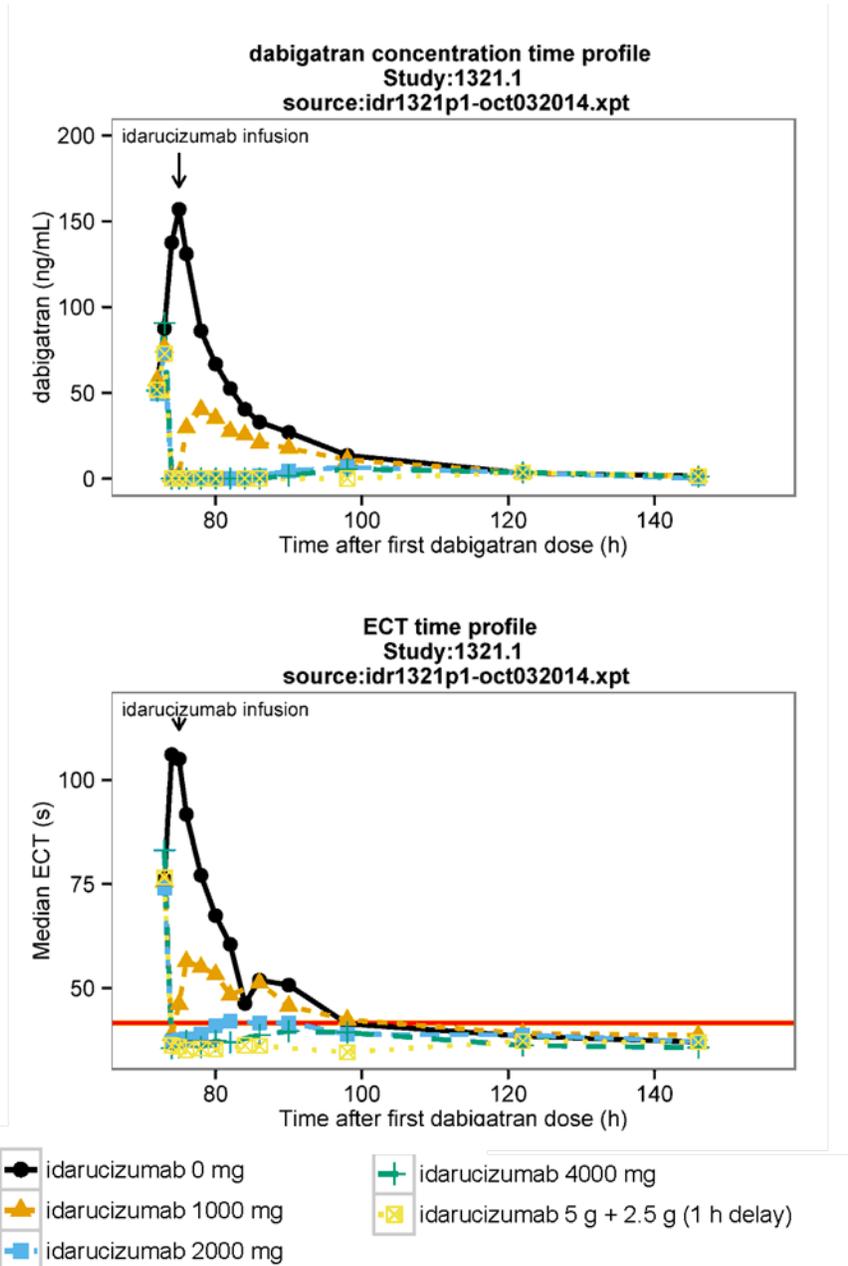
Based on the above observations, it is reasonable to conclude that idarucizumab doses >4 g are required to achieve immediate and sustained restoration of ECT measures to baseline.

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<sup>2</sup> <http://www.hematology.org/Clinicians/Guidelines-Quality/Quick-Ref/2869.aspx>

These observations formed the basis for the applicant's selection of an idarucizumab dose of 5 g for subsequent studies.

**Figure 2. Median dabigatran concentration time profiles and ECT response in healthy male volunteers following placebo or idarucizumab doses ranging from 1 to 7.5 g**



Note: Lines show mean concentration time profile for unbound total dabigatran (top figure) and mean ecarin clotting time (ECT) following 1, 3, 5, 7.5 g idarucizumab or placebo in healthy male volunteers. The red lines indicate the mean + 2 standard deviations of baseline ECT. Dabigatran 220 mg was administered twice daily on Days 1 – 3 and 220 mg once daily on Day 4.

#### 2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

There was insufficient information available from the healthy volunteer studies to conduct exposure-response safety analyses for idarucizumab. The most common adverse events observed during the treatment period from these studies were headaches (12 subjects, 5%), skin irritations (6 subjects, 3%), dizziness (5 subjects, 2%), and back pain (4 subjects 2%). No serious adverse events or deaths occurred on treatment with idarucizumab during these studies, but there is currently limited clinical experience with use of idarucizumab. For an overview of safety, please refer to Dr. Dmytrijuk's medical review.

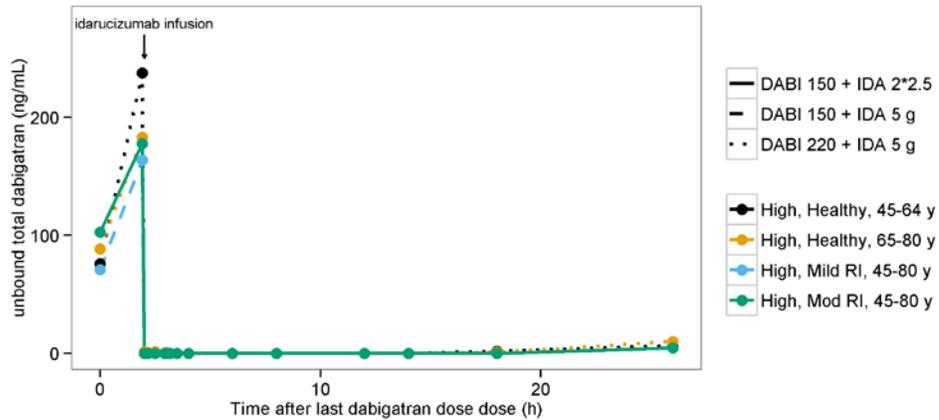
#### 2.2.4.3 Does this drug prolong the QT or QTc interval?

Idarucizumab is a fragment of a humanized murine monoclonal antibody. The molecular weight is 47 kDa, which will limit the ability of this compound to directly inhibit cardiac currents.

#### 2.2.4.4 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

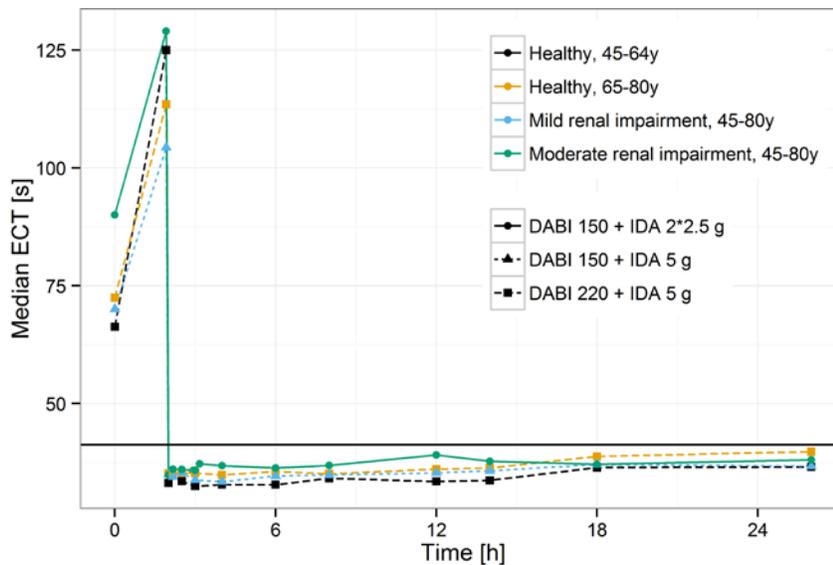
Yes. The proposed idarucizumab dose is supported by multiple studies the applicant conducted in healthy subjects and an open-label case series in patients (see Table 1). Available data suggests that the proposed 5 g dose is sufficient to achieve immediate and sustained dabigatran suppression resulting in a reversal of coagulation markers to baseline levels in a majority of the subjects including elderly and subjects with mild or moderate impairment of renal function (Figures 3 and 4). The effects of idarucizumab were demonstrated at dabigatran concentrations that are comparable to those observed in the original dabigatran registration trials for the treatment of venous thromboembolism and the prevention of stroke in patients with atrial fibrillation (details presented in the Pharmacometrics Review).

**Figure 3. Median dabigatran concentration time profiles in subjects over and under 65 years of age, with normal or impaired (mild or moderate) renal function following a 5 g idarucizumab dose**



Note: Colors indicate the study population; line type indicates the dabigatran b.i.d. dose (DABI) in milligrams and the idarucizumab dose (IDA) in grams. The IDA 2.5\*2-arm received two doses of 2.5 g idarucizumab 1 h apart. Only arms with the proposed idarucizumab dose are shown in the figure.

**Figure 4. Median ECT time profiles in subjects over and under 65 years of age, with normal or impaired (mild or moderate) renal function following a 5 g idarucizumab dose.**



Note: Time 0 represents pre-dose median ECT at steady-state with dabigatran. The reference line represents mean + 2 standard deviations of baseline ECT. Colors indicate the study population; line type indicates the dabigatran b.i.d. dose (DABI) in milligrams and the idarucizumab dose (IDA) in grams. The IDA 2.5\*2-arm received two doses of 2.5 g idarucizumab 1 h apart. Only arms with the proposed idarucizumab dose are shown in the figure

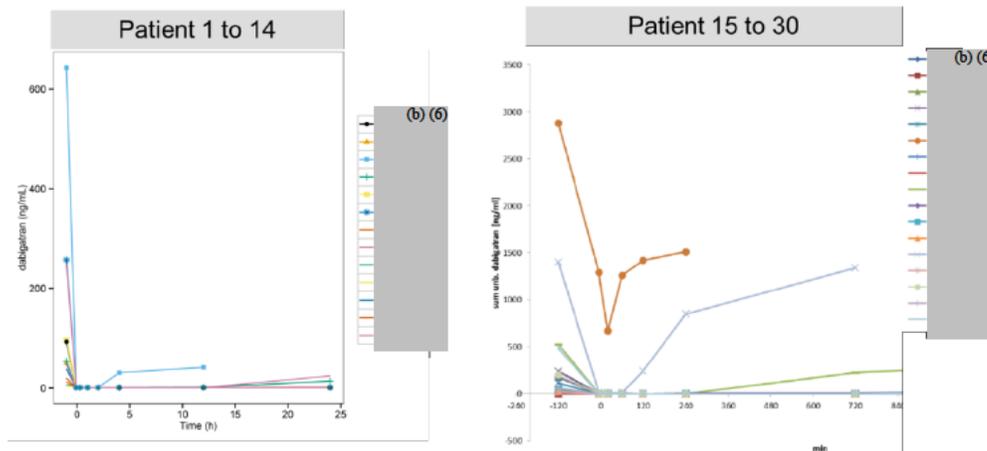
Source: Study 1321.2, datasets pk4p.xpt and pd4p.xpt

However, results from the healthy volunteer studies and the ongoing Phase 3 study suggest that some patients will not achieve immediate or sustained suppression with the proposed 5 g idarucizumab dose. In these patients administration of an additional dose may be required. The review team discusses the scenarios when immediate and sustained suppression may not be achieved below.

**Situation when immediate suppression may not be achieved:**

At high dabigatran concentrations (pre-idarucizumab administration), dabigatran levels may not be adequately suppressed by a 5 g idarucizumab dose. Evidence to this end was obtained from study 1321.3, an open label phase 3 trial enrolling patients treated with dabigatran who have uncontrolled bleeding (Group A) or require emergency surgery or medical procedures (Group B). Preliminary data from 30 patients are shown in Figure 5.

**Figure 5. Preliminary data from the ongoing phase 3 trial (1321.3)**



Source: Left panel: Study report 1321.3 table 15.6.1:2 and 15.2.13:1, Right panel: adapted from Applicant's orientation slides 4/13/2015

Note: Concentration time profile for unbound total dabigatran before (Time <0) and after (Time ≥0) administration of 5 g idarucizumab.

The following is inferred from the observed data:

- A 5 g idarucizumab dose was inadequate to suppress dabigatran in one patient (ID# (b) (6)) with plasma concentrations close to 3000 ng/mL.
- Out of 30 patients, 3 had unbound sum dabigatran concentrations above 600 ng/mL. Based on the applicant's orientation slides from April 13, 2015, less than 1% of patients with atrial fibrillation receiving treatment with dabigatran are expected to have peak concentration of unbound sum dabigatran >560 ng/mL (observations from 1160.26 [RE-LY]).

### **Situation when sustained suppression may not be achieved:**

In the Phase I study in subjects with mild and moderate renal impairment, unbound sum dabigatran concentrations ranging between 6-12 ng/mL and 6-46 ng/mL, respectively, were observed post-idarucizumab (5 g dose) administration. One subject in the moderate renal impairment group (subject ID 703) had unbound sum dabigatran concentration return to 46 ng/mL approximately 24 hours after idarucizumab administration. All the changes in unbound sum dabigatran were associated with a corresponding change in dTT. Without overt signs of bleeding, the clinical significance of these elevations is not clear, but these observations support that a 5 g dose may not be sufficient in all patients to achieve sustained dabigatran suppression.

This was clearly illustrated in one patient (ID # (b) (6)) from the open-label phase 3 study who had pre-dose unbound sum dabigatran concentrations ~ 1400 ng/mL. In this patient, a 5 g idarucizumab dose was able to initially suppress dabigatran, however, unbound sum dabigatran concentrations returned to 848 ng/mL at approximately 4 h after idarucizumab administration and continued to increase to 1340 ng/mL at approximately 12 h after idarucizumab dose. Corresponding increases in dTT were also noted. No observations are available after 12 h in this subject.

Similar findings are also reported in the applicant's publication of interim study results<sup>3</sup> and in the applicant's 120-day safety update where 16 out of 90 patients treated with idarucizumab had increased coagulation markers after initial suppression. This included two cases where patients received a second idarucizumab dose due to elevated coagulation markers and clinical signs of bleeding (Patients IDs (b) (6) and (b) (6)).

### **Mechanistic explanation for the redistribution peak and labeling proposal:**

Idarucizumab is able to immediately bind and render ineffective available dabigatran in the systemic circulation upon administration. Once idarucizumab binds available dabigatran, the equilibrium between 'available' and 'unavailable' dabigatran shifts. In turn, this forces an influx of dabigatran from deep peripheral tissues into the systemic circulation. However, by the time dabigatran redistributes from peripheral tissue, most remaining unbound idarucizumab is eliminated and unable to bind with dabigatran. This is a result of idarucizumab's pharmacokinetics described above (rapid initial half-life of 45 min). This redistribution from peripheral tissues is the cause of dabigatran peaks observed following idarucizumab administration in the Phase 1 PK-PD trials as well as in the ongoing Phase 3 observational study. The timing of the redistribution as well as the likelihood of its occurrence depends on the initial dabigatran concentrations.

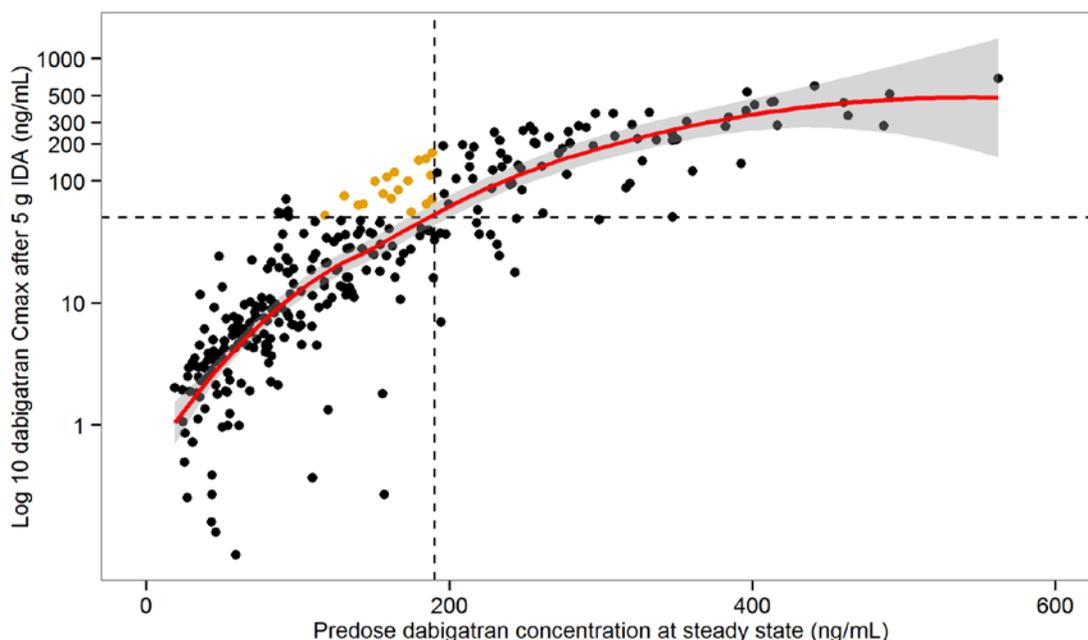
An unbound sum dabigatran concentration >50 ng/mL is very likely to be detectable using any of the four coagulation markers and thus represents a reasonable threshold representing dabigatran-induced anticoagulant activity. The likelihood that either aPTT or ECT will be above the upper limit normal of the reference range at sum unbound dabigatran

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<sup>3</sup> Pollack et al. New England Journal of Medicine, 2015;373:511-520

concentration >50 ng/mL is 97.1 to 99.7%. This threshold also approximates the average pre-dose concentrations observed in RE-LY for the 150 mg BID dose group. Based on the reviewers' analysis (Figure 6), a pre-dose sum unbound dabigatran concentration above 190 ng/mL (292 ng/mL sum dabigatran) is likely to result in redistribution post idarucizumab treatment that meets this threshold.

**Figure 6. Simulated Steady-State Unbound Sum Dabigatran Trough Concentrations Versus The Maximum Re-Distribution Unbound Sum Dabigatran Concentration**



Note: Pre-dose steady state unbound sum dabigatran trough concentrations (x axis) are plotted versus the maximum unbound sum dabigatran concentration after idarucizumab infusion. The circles represent individual data. The red line is a non-parametric smoother (loess) used for illustration purposes. The shaded area is the 95% CI around the loess line. The horizontal dashed line represents the 50 ng/mL cut off. The vertical dashed line denotes the 190 ng/mL cut off.

Source: Simulated based on applicant's model run2113.mod

It should be noted that based on the Phase 3 dabigatran registration trial (RE-LY), 10% of patients had pre-dose sum unbound dabigatran concentrations  $\geq 213$  ng/mL (sum dabigatran 328 ng/mL).

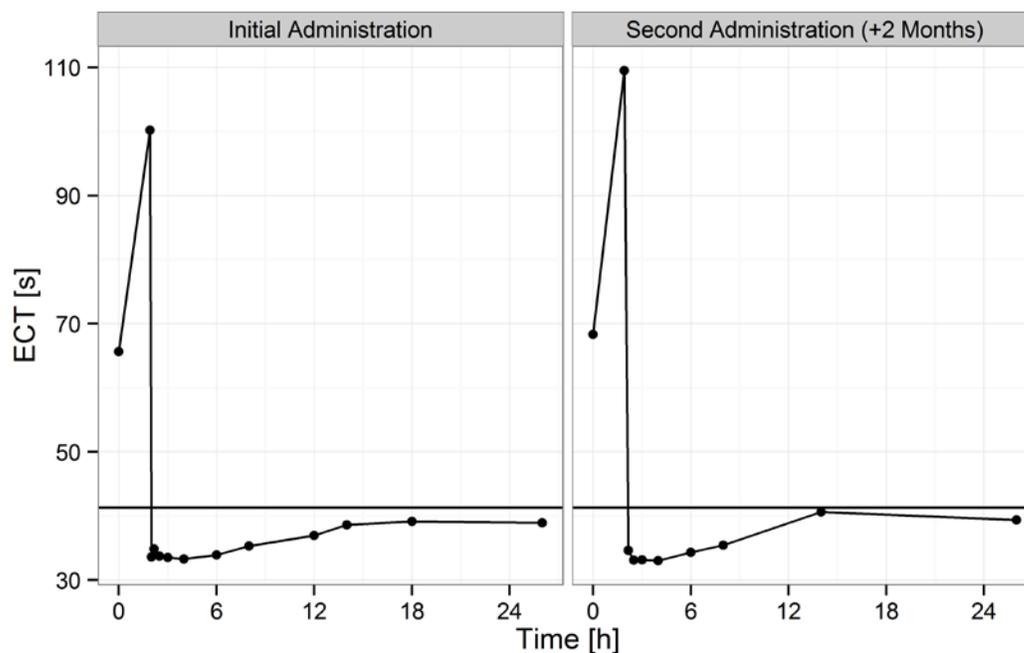
In summary, the clinical pharmacology review team concludes that the redistribution peak may occur at an appreciable rate in clinical practice (>10%) to warrant communication of this finding in the idarucizumab labeling. The team concludes that predicting the timing of the peak may not be feasible, but that available clinical tests of coagulation that would be in use for these patients can identify such situations. In addition, the clinical pharmacology review proposes that re-dosing of idarucizumab be considered in patients who continue to exhibit elevated coagulation parameters with reappearance of clinically relevant bleeding. So far

there is no identified risk associated with re-administration of idarucizumab that would greatly outweigh the potential benefit. Further, there is some experience with re-administration of idarucizumab in Phase I (see Question 2.2.5) as well as Phase 3 (described previously). The additional dosing consideration represents a practical and low risk approach for addressing the subset of patients for which a single 5 g idarucizumab dose is insufficient. The clinical pharmacology review team has outlined their support for this proposal on multiple occasions, including the Application Scoping Meeting (April 14, 2015), Mid-Cycle Meeting (May 15, 2015), and as part of the Late-Cycle Communication (DARRTS date: July 27, 2015) to the sponsor, and recommends that flexible language be included in the idarucizumab labeling to reflect this option.

### 2.2.5 Is the effect of idarucizumab reproducible upon repeat administration?

Yes. In a study in healthy subjects, receiving dabigatran 220 mg BID, a second administration of idarucizumab about 2 months after the first administration demonstrated the reproducibility of idarucizumab to reverse dabigatran-induced anticoagulation upon repeat administration as shown in Figure 7.

**Figure 7. Time course for median ECT following initial administration of 2.5 g of idarucizumab and repeat administration in healthy subjects at steady-state with 220 mg BID dabigatran.**



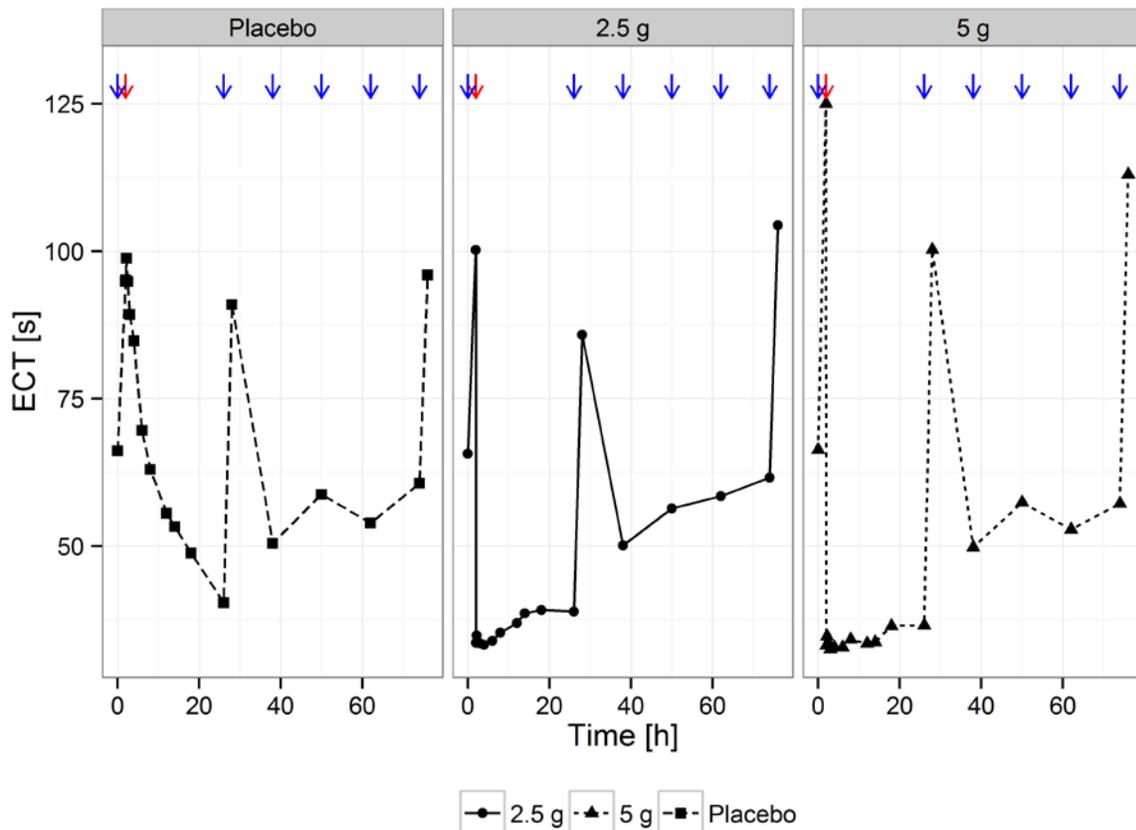
Note: Time 0 represents pre-dose mean ECT at steady-state with 220 mg BID of dabigatran. The reference line represents mean + 2 standard deviations of baseline ECT.

Source: Study 1321.2, dataset pd4p.xpt

### 2.2.6 When can dabigatran be re-initiated after treatment with idarucizumab?

In most patients who are indicated to continue treatment with dabigatran, re-initiation of treatment within a reasonable time frame will be necessary to prevent thrombotic events. A dedicated study in healthy subjects shows that re-initiation of dabigatran 24 h after idarucizumab administration resulted in similar unbound sum dabigatran exposures. The coagulation times before and after the idarucizumab or placebo treatment were also comparable (see Figure 8) supporting re-initiation as early as 24 hours after treatment with idarucizumab.

**Figure 8. Comparison of the median ECT time profile following the administration of placebo, 2.5 g, and 5.0 g idarucizumab and upon re-initiation of dabigatran.**



Note: Blue arrows represent tie time of dabigatran administration; the red arrow represents the administration of idarucizumab.

Source: Study 1321.2, dataset pd4p.xpt,

### 2.2.7 What are the PK characteristics of idarucizumab?

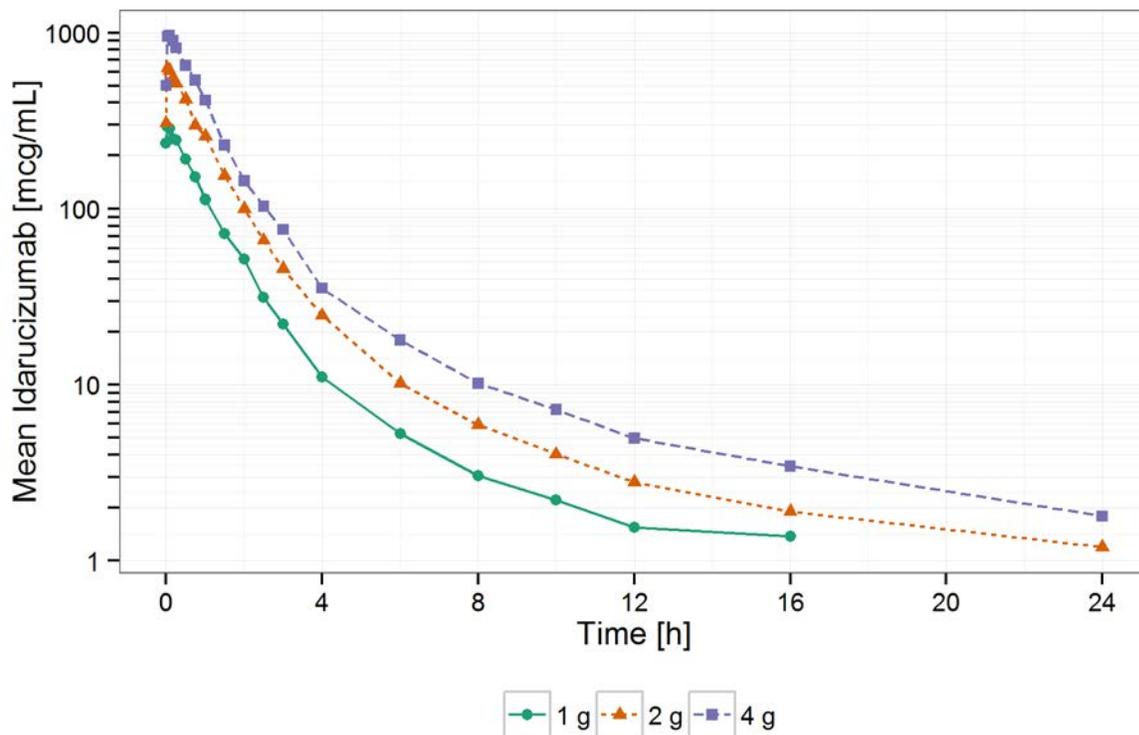
Idarucizumab shows dose proportional pharmacokinetics in the studied range (20 to 80,000 mg). The time course of the drug in plasma can be well described by a two-compartment

model, where the drug shows a fast initial distribution half-life of around 45 min followed by an elimination half-life of about 8-11 h.

#### 2.2.7.1 What are the single dose and multiple dose PK parameters?

Idarucizumab has been studied in healthy subjects after a 1 h infusion and 5 min bolus i.v. administration. AUC increases proportionally with dose in the studied range from 20 mg to 8 g. The initial half-life of idarucizumab is on average around 45 minutes, while the terminal half-life was on average 30 h at clinically relevant doses. The initial half-life determines the effective half-life, because the majority of exposure is eliminated within the first 4 to 6 h (Figure 9). Mean residence time of idarucizumab at doses from 1.2 to 8 g was 2-2.5 h. Idarucizumab PK is not altered by exposure to dabigatran at steady-state (Tables 2 and 1324).

**Figure 9. Mean idarucizumab concentrations after 5 min bolus administration**



Source: Study 1321.1, dataset: pk4p.xpt

**Table 2. Arithmetic mean (CV%) PK parameters after 5-min infusion with idarucizumab**

Dose [g]	AUC <sub>0-4</sub>	AUC <sub>4-8</sub>	AUC <sub>8-12</sub>	AUC <sub>12-24</sub>	AUC <sub>inf</sub>	C <sub>max</sub>	*t <sub>max</sub>
1	6930 (9.88)	508 (46.7)	189 (38.7)	188 (49.4)	7850 (13.9)	6430 (17.3)	0.12 (0.08, 0.17)
2	14500 (16.7)	1050 (17.5)	352 (20.9)	428 (26.9)	16600 (16.3)	13900 (23.1)	0.14 (0.12, 0.25)
4	22800 (22.8)	1690 (23.1)	622 (22.6)	776 (20.3)	26300 (21.7)	21500 (12.9)	0.17 (0.12, 0.25)

Source: Study 1321.1 pk6p.xpt

**Table 3. Arithmetic mean (CV%) PK parameters after 5-min infusion with idarucizumab at steady state dabigatran exposure**

Dose [g]	AUC <sub>0-4</sub>	AUC <sub>4-8</sub>	AUC <sub>8-10</sub>	AUC <sub>10-12</sub>	AUC <sub>12-24</sub>	AUC <sub>inf</sub>	C <sub>max</sub>	*t <sub>max</sub>
1	5860 (17.9)	360 (28.3)	83.9 (27)	60.1 (28.5)	159 (44.9)	6570 (18.9)	5450 (13.6)	0.12 (0.08, 0.17)
2	14500 (11.7)	976 (33.5)	203 (29.6)	156 (26.1)	533 (19.8)	16700 (11.2)	12800 (21.1)	0.2 (0.17, 0.33)
4	27500 (15.7)	1640 (17.1)	366 (13)	274 (13.5)	863 (11.7)	31100 (14.3)	26500 (24.3)	0.12 (0.08, 0.17)

Source: Study 1321.1 pk6p.xpt

2.2.7.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable. At the time of review, individual level data was available from healthy and renal impairment subjects. An open-label clinical study is still ongoing. No comparison is possible at this time.

2.2.7.3 What are the characteristics of drug distribution?

Volume of distribution at steady-state was on average 5-8 L when assessed by non-compartmental analysis, which suggests that it is mostly present in interstitial fluid. The estimate is similar to that obtained from population PK analysis, which was about 9.2 L. Idarucizumab does not bind to human serum albumin.

2.2.7.4 Does the mass balance study suggest renal or hepatic as the major route of elimination?

A mass balance study was not performed. Typically, monoclonal antibodies are metabolized and excreted urine.

#### 2.2.7.5 What are the characteristics of drug metabolism?

Idarucizumab is an antibody fragment. The expectation is that these types of compounds are degraded to peptides and amino acids. Involvement of cytochrome P450 or other enzymes frequently related to drug metabolism is unlikely.

#### 2.2.7.6 What are the characteristics of drug excretion?

The mean clearance of idarucizumab was 40 mL/min based on compartmental analysis. Renal excretion of unchanged idarucizumab was dose-dependent and ranged from 8 to 40% of idarucizumab doses from 1 to 8 g. Proteins catabolism and reabsorption occurs at the tubular level. It is possible that some of these mechanisms are saturable, which could explain the dose related increase in unchanged protein. In patients with mild and moderate renal impairment, the fraction of idarucizumab excreted unchanged was similar, for a given dose level, to that of healthy subjects.

#### 2.2.7.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Idarucizumab shows dose-linear PK in the range from 20 mg to 8 g.

#### 2.2.7.8 How do the PK parameters change with time following chronic dosing?

Not applicable. Since idarucizumab is intended for the immediate reversal of dabigatran action in cases of bleeding and emergency surgery, the individual administrations will occur over a limited time range.

In the submitted PK/PD studies, there was no effect on PK when idarucizumab was re-dosed within one hour of the original dose, or after 2 months of the original dose. The potential for immunogenicity is low and will be discussed in the review by Office of Biological Products.

#### 2.2.7.9 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Inter-subject variability, reported as coefficient of variation (CV%), of AUC ranged from 10 to 21%, which is not considered large.

### 2.3 Intrinsic Factors

#### 2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

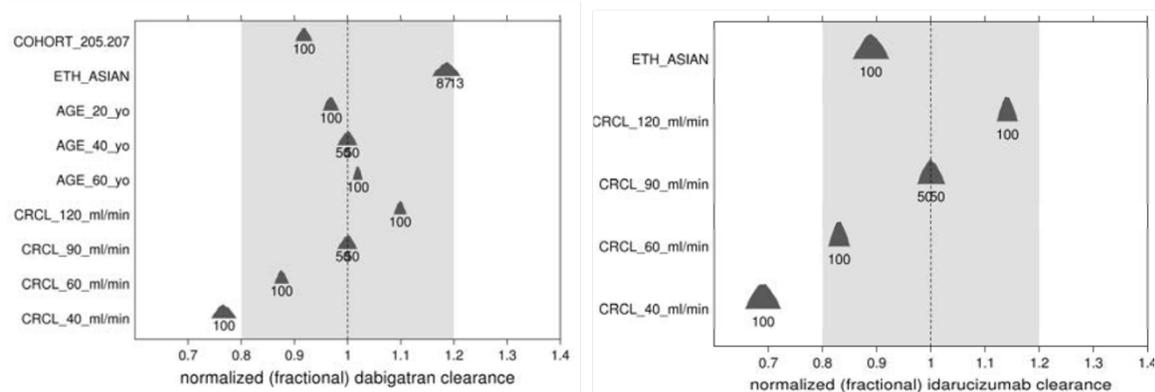
Renal function, is the dominant intrinsic factor influencing exposure of both dabigatran and idarucizumab. Study 1321.2 enrolled subjects with normal renal function as well as subjects with mild and moderate renal impairment. A reduction in CrCL from 90 mL/min (the population median) to 40 mL/min resulted in 32% higher dabigatran exposure, measured by AUC. Similarly, a reduction in CrCL from 90 mL/min to 40 mL/min resulted in 45% higher idarucizumab exposure, measured by AUC (Figure 10).

Because renal function affects both drugs with similar magnitude and same direction, no difference in the ability of idarucizumab to eliminate dabigatran from systemic circulation was observed. Therefore, there is no need to adjust for renal function when administering idarucizumab.

Japanese subjects were found to have 11% lower CL resulting in 11% higher AUC, Figure 10. This difference is not considered to be clinically meaningful.

Please refer the Pharmacometrics Review for further discussion regarding intrinsic factors.

**Figure 10. Covariates affecting exposure of dabigatran and idarucizumab**



*Note:* Plots depict the estimate of covariate effects on dabigatran and idarucizumab clearance, taking into account uncertainty in fixed effects parameters. Covariate effects are expressed normalized to a typical, population average reference clearance. Exposure (AUC) is computed by  $AUC = \text{Dose} / \text{Clearance}$ . Normalized fractional dabigatran clearance of 1 equals 87.2 L/h. Normalized fractional idarucizumab clearance of 1 equals 2.32 L/h.

*Source:* Applicant's modeling and simulation report Figure 10.1.2: 1

### 2.3.2 Based upon what is known about exposure-response relationships what dosage regimen adjustments, if any, are recommended?

At this time there are no dose adjustments necessary based on intrinsic factors. Gender and age did not influence the exposure of idarucizumab. The impact of renal impairment and race is explained in Section 2.3.1. Idarucizumab has not been studied in pregnant women and subjects with hepatic impairment.

## 2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effect of idarucizumab on drug metabolizing enzymes and transporters has not been studied *in vitro* or *in vivo*, except for assessments of binding of anticoagulants and antiplatelet agents to idarucizumab.

2.4.2 Drug-drug interactions

Idarucizumab is an antibody fragment, which is likely metabolized by proteases and excreted renally. It is also not a cytokine modulator.

In vitro assessment of the effect of idarucizumab on commonly administered anticoagulants and antiplatelet agents showed no interaction with the direct factor Xa inhibitors rivaroxaban and apixaban. Likewise, no interaction was observed with hirudin and argatroban, heparin, and warfarin.

## 2.5 General Biopharmaceutics

Idarucizumab drug product is available as a 50 mg/mL solution for injection in a 50 mL vial. Therefore, one vial contains 2.5 g idarucizumab, or half of the labelled dose of 5 g for one application. The solution also contains 25 mM sodium acetate/acetate (b) (4), 220 mM sorbitol, and 0.2 g/L polysorbate 20. The pH is adjusted to 5.5.

The drug is supposed to be administered without dilution in a (b) (4) bolus injection.

## 2.6 Analytical section

2.6.1 What moieties were quantified?

Idarucizumab was identified in plasma and urine as total moiety, i.e. the assay did not distinguish between idarucizumab with a dabigatran load, and free dabigatran.

Dabigatran was assessed as unbound (free) and sum dabigatran, which means that both the parent compound and the acyl-glucuronide were assessed together after hydrolysis. Since both the parent and glucuronide are active, this is considered the relevant species for assessment. Free moieties were assessed using ultrafiltration prior to sample preparation. Tables 4 and 5 summarize the characteristics of each method.

2.6.2 What are the characteristics of the analytical methods?

Idarucizumab

**Table 4. Description of idarucizumab analytical methods**

Parameter	Idarucizumab in Plasma	Idarucizumab in Urine
Method	Sandwich ELISA	
Matrix	Human plasma	Human urine
Analyte	BI 655075 (idarucizumab)	
Quantitation Range	1,000 to 10,000 ng/mL	
Interference	None	None
Accuracy / Precision		
LLOQ	3.5% / 10%	8.9% / 8.6%
ULOQ	3.3% / 14.2%	-1.6% / 5.6%
Stability		
Benchtop	28 h	28 h
Freeze/Thaw	6 cycles	6 cycles
Freezer	12 months	6 months
QC Plan	4/6 QC meet requirement	

Dabigatran

**Table 5. Description of dabigatran analytical methods**

Parameter	SUM Dabigatran	SUM Unbound Dabigatran	
Method		HPLC/MS-MS	
Matrix	Plasma (EDTA)	Urine	Plasma (EDTA)
Analyte		Dabigatran (BIBR 953 ZW)	
Quantitation Range	5.00 – 5000 ng/mL	20.0 to 10,000 ng/mL	1.00 to 400 ng/mL
Interference		None	
Accuracy / Precision			
LLOQ	1.6% / 6.8%	9.8% / 4.2%	9.0% / 3.5%
ULOQ	-0.6% / 1.9%	1.6% / 1.3%	1.0% / 0.9%
Stability			
Ice bath	6 h	6 h	6 h
Freeze/Thaw	3 cycles	3 cycles	3 cycles
Autosampler	5 days	26 h	6 days
Long term	214 days	101 days	147 days
QC Plan	2/3 of QC within $\pm 15\%$ (20% at LLOQ) of nominal value; 50% of QCs at same concentration		

An audit of the idarucizumab analytical site (b) (4) will be conducted. Clinical sites and sites where dabigatran samples were analyzed had recent successful audits related to

other submissions and were therefore not audited again (DNDBE/OSIS memorandum, DARRTS date 06/12/2015).

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/s/  
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