ORIGINAL ARTICLE

jth

Pharmacokinetics of idarucizumab and its target dabigatran in patients requiring urgent reversal of the anticoagulant effect of dabigatran

Stephan Glund[1] | Kelly Coble[2] | Dietmar Gansser[1] | Joachim Stangier[1] |
Karin Hoermann[1] | Charles V. Pollack[3] | Paul Reilly[2]

[1]Boehringer Ingelheim Pharma GmbH and Co. KG, Biberach an der Riss, Germany

[2]Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut

[3]Thomas Jefferson University, Philadelphia, Pennsylvania

Correspondence
Stephan Glund, Boehringer Ingelheim Pharma GmbH and Co. KG, Birkendorfer Strasse 65, 88397 Biberach an der Riss, Germany.
Email: stephan.glund@boehringer-ingelheim.com

Funding information
This study was planned and conducted by Boehringer Ingelheim.

Abstract

Background: Idarucizumab is a monoclonal antibody fragment that reverses dabigatran anticoagulation. Pharmacokinetics (PK) of idarucizumab have been described in healthy, elderly, or renally impaired (RI) volunteers, but PK data in patients are lacking.

Objectives: This analysis describes the PK of idarucizumab and its target dabigatran in bleeding/surgical patients.

Patients and Methods: Results from the Reversal Effects of Idarucizumab on Active Dabigatran study, a prospective, multicenter, single-arm study demonstrated the reversal of dabigatran anticoagulation by idarucizumab in patients with uncontrollable bleeding (group A) or who needed urgent surgery (group B). Idarucizumab and unbound dabigatran concentrations, immunogenicity, and pharmacodynamics were assessed.

Results: Total and unbound dabigatran levels at baseline were 165 ng/mL vs 110 ng/mL and 103 ng/mL vs 69.5 ng/mL in group A and B patients, respectively. Maximum plasma concentrations and area under the curves (AUC_{0-24}) of idarucizumab in group A vs B, respectively, were 24 900 nmol/L vs 25 000 nmol/L and 76 600 nmol/h/L vs 68 000 nmol/h/L. Idarucizumab AUC_{0-24} increased by 38% in mild, 90% in moderate, and 146% in severe RI patients vs normal renal function. Hepatic impairment or geographical region had no relevant effect on idarucizumab PK. Idarucizumab immediately decreased unbound dabigatran concentration (<20 ng/mL). A linear correlation was observed between unbound dabigatran and diluted thrombin time and ecarin clotting time. Antidrug antibody titers were low (1-64 at day 30; 0-16 at day 90) and had no impact on idarucizumab PK and pharmacodynamics.

Conclusion: Idarucizumab PK in target patients was consistent with phase I data. Patient characteristics had no impact on PK, whereas RI increased the exposure of idarucizumab and dabigatran.

Trial registration number: ClinicalTrials.gov NCT02104947.

1 | INTRODUCTION

The management of stroke prevention in atrial fibrillation has been improved with the introduction of direct-acting oral anticoagulants[1,2]; however, as with all anticoagulants, direct-acting oral anticoagulant use is associated with an increased risk of bleeding.[3] There is therefore a need for reversal agents for bleed management. Idarucizumab is a humanized monoclonal antibody fragment that specifically inhibits the anticoagulant effect of dabigatran and has been approved for use in adults.[4,5]

Idarucizumab reverses the treatment effects of dabigatran and provides an option for patient management during rare emergency situations. Results from the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD) study confirmed the rapid and complete reversal of the effects of dabigatran anticoagulation by idarucizumab in patients with life-threatening or uncontrolled bleeding, or in those requiring urgent surgery.[6] The pharmacokinetics (PK) were not described.

The PK of idarucizumab has been evaluated in phase I trials in healthy volunteers, and in elderly and renally impaired (RI) subjects.[7,8] In these trials, idarucizumab infusion following dabigatran administration reduced the unbound and active dabigatran concentrations to the lower limit of quantification (1 ng/mL).[7] The PK of idarucizumab was shown to be unaffected by age in older otherwise healthy subjects. However, impaired renal function in these subjects resulted in decreased idarucizumab clearance (normal: 47.1 mL/min vs mild RI: 32.8 mL/min vs moderate RI: 25.7 mL/min) and prolonged initial half-life (up to 49%). Consequently, total exposure to idarucizumab increased up to 84%.[8] In phase I studies, based on antidrug antibody (ADA) detection, there was a modest immunogenic effect of idarucizumab with no detectable effect of pre-existing ADA on the PK of idarucizumab or its pharmacologic effect.[9]

Here we describe the PK of idarucizumab and unbound dabigatran in patients from the RE-VERSE AD study patient cohort, and investigate the effect of patient characteristics on the PK and pharmacodynamics (PD) of idarucizumab. We have also evaluated ADA formation in the target patient population.

2 | METHODS

2.1 | Study design and participants

The study design, study treatment, and idarucizumab dose selection have been explained in detail elsewhere.[5,6] Briefly, RE-VERSE AD was a multicenter, prospective, open-label study that included patients aged ≥18 years who presented with uncontrolled or life-threatening bleeding (group A) or who were required to undergo surgery or other invasive procedures with a risk of bleeding (group B) that could not be delayed for ≥8 hours. All patients received 5 g of intravenous idarucizumab administered as two 50-mL bolus infusions each containing

Essentials

- Idarucizumab PK has been described in healthy volunteers, elderly and renally impaired subjects.
- PK of idarucizumab and its target dabigatran was assessed in patients.
- Hepatic function and ADAs had no impact on idarucizumab PK; but renal impairment altered the PK.
- Idarucizumab/dabigatran PK in patients is similar to healthy volunteers.

2.5 g of idarucizumab ≤15 minutes apart. The study was carried out in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonisation. Each patient or their authorized representative provided written informed consent.

2.2 | Procedures

The PK and PD assessments were performed as described by Pollack et al.[6] Briefly, blood samples for PK and PD assessments were obtained at baseline, after the first infusion of idarucizumab, and between 10 and 30 minutes and at 1, 2, 4, 12, and 24 hours after the second infusion. Analyses of coagulation assays (dilute thrombin time [dTT; Hemoclot, Hyphen BioMed, Neuville sur Oise, France] and ecarin clotting time [ECT; in-house assay, 6 U/mL ecarin; Pentapharm, Basel, Switzerland]) was done using validated assays at Menal GmbH (Emmendingen, Germany)[10]; concentrations of idarucizumab as well as unbound and total dabigatran were estimated at a central laboratory as described previously.[6,8] Unbound dabigatran was defined as the fraction of dabigatran that was neither bound to idarucizumab nor plasma proteins, and which is an approximate measure of pharmacologically active dabigatran. Total dabigatran was defined as bound and unbound dabigatran. Both total and unbound dabigatran included the active metabolites in plasma. Idarucizumab PK parameters were determined by noncompartmental analysis using Phoenix WinNonlin. The area under the curve between 0 and 24 hours (AUC_{0-24}) was only calculated if the concentration measurement at 24 hours, as well as at least one of the two measurements at planned time—4 and 12 hours—was available. The maximum concentration (C_{max}) and the time from the start of the infusion to achieve maximum concentration were only determined if all values at the planned times of 20 minutes (ie, between 10 and 30 minutes), 1 and 2 hours after the end of the second infusion were available. Unbound dabigatran concentrations determined as "below the limit of quantification" were replaced by a value of 1 ng/mL, reflecting the value of the lower limit of quantification. The dabigatran concentrations are represented in ng/mL to allow comparison with historical data. Idarucizumab concentrations are reported in nmol/L.

Renal function category based on creatinine clearance (CrCl) was calculated by using the Cockcroft-Gault formula and the following cutoffs: normal, CrCl ≥80 mL/min, mild RI, CrCl ≥50 to <80 mL/min, moderate RI, CrCl ≥30 to <50 mL/min and severe RI, CrCl <30 mL/min. For assessment of liver function, the frequency of patients with elevated aspartate transaminase and alanine transaminase or bilirubin was tabulated.

2.3 | Outcomes

The concentrations of idarucizumab as well as unbound dabigatran were assessed at prespecified time points. For total dabigatran, concentration before first idarucizumab administration was determined.

2.4 | Anti-idarucizumab antibodies

Samples to determine the presence of ADAs against idarucizumab were taken at baseline (before administration), on days 30 and 90 after idarucizumab administration. ADAs were detected in human plasma samples by a validated bridging electrochemiluminescence method (Covance Laboratories Inc., Chantilly, Virginia), as described elsewhere.[9] The specificities of the ADA for different idarucizumab epitopes were assessed in a competitive-format electrochemiluminescence assay. Two molecules were used: a full-length immunoglobulin G1 molecule containing two idarucizumab Fab fragments (molecule 1) and a Fab with constant regions C_H1 and C_L identical to those in idarucizumab, but with different variable regions (molecule 2). Blocking by molecule 1 only would suggest that an ADA was binding to variable regions of idarucizumab; blocking by both molecules would be indicative of an ADA binding to the constant regions or binding with a mixed specificity; and blocking by molecule 2 only would suggest that an ADA was binding to an epitope near the C-terminus of idarucizumab (although this would be an ADA that is disrupted by the presence of C_H2 and C_H3 in molecule 1).

2.5 | Statistical analysis

The PK analyses were summarized descriptively (geometric mean [gMean], unless otherwise stated). The relationship between plasma concentration of unbound dabigatran and its active metabolites and clotting variables are described by linear regression modeling.

3 | RESULTS

3.1 | PK of idarucizumab

3.1.1 | By patient group

The plasma concentration–time profile of idarucizumab was similar between bleeding (group A) and surgical (group B) patients. After
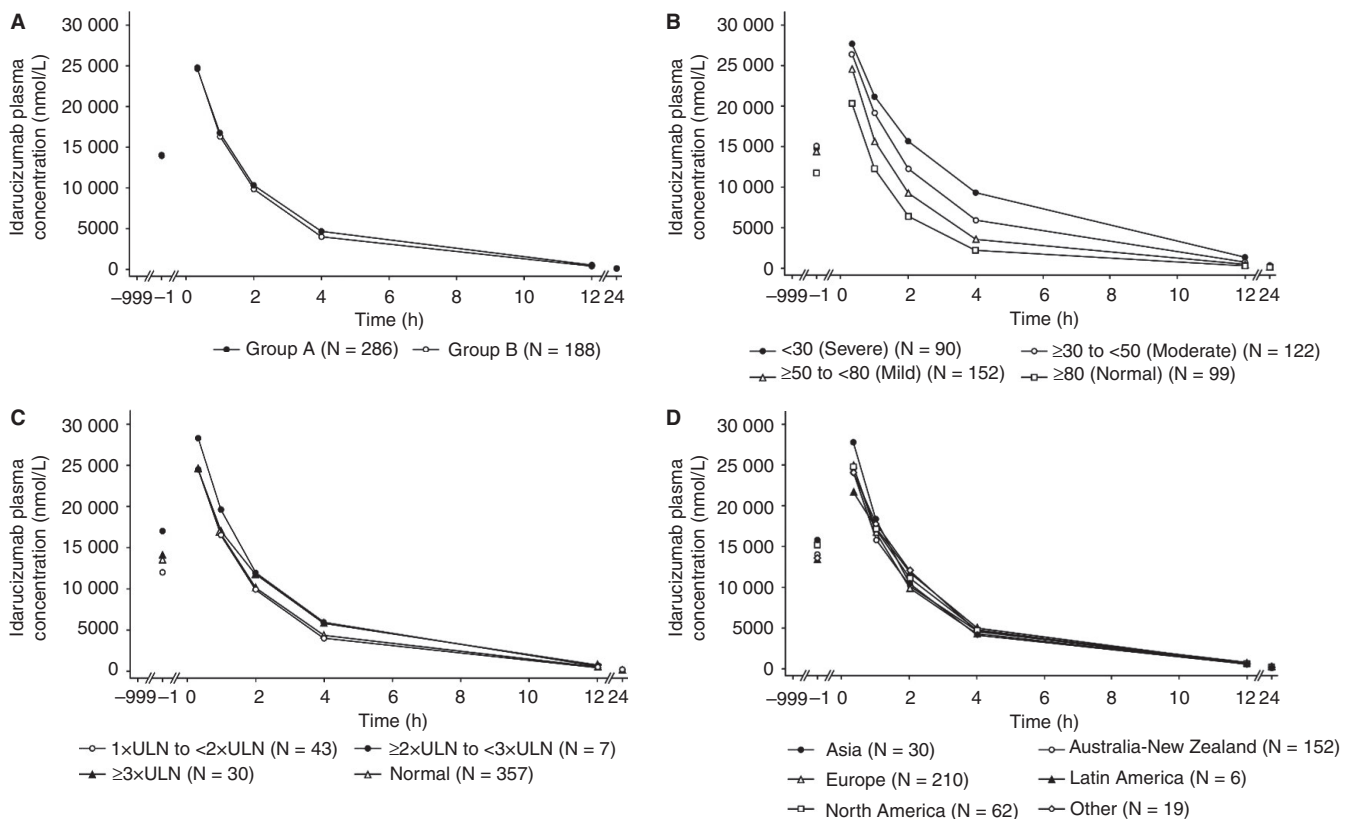

FIGURE 1 Geometric mean plasma concentration–time profiles of idarucizumab following administration of idarucizumab 5 g in (A) patients from group A and group B; (B) patients who are renally impaired; (C) patients with hepatic impairment; and (D) in patients from different regions

completion of the second infusion, the concentration of idarucizumab rapidly declined. The gMean concentrations 12 and 24 hours after idarucizumab administration were 529 and 133 nmol/L in group A, respectively, and 429 and 107 nmol/L in group B, respectively (Figure 1A). C_{max} was 24 900 nmol/L vs 25 000 nmol/L and the gMean AUC_{0-24} was 76 600 nmol/h/L vs 68 000 nmol/h/L, for group A and B, respectively.

3.1.2 | By renal impairment

The concentration–time profile of idarucizumab in patients by renal function is illustrated in Figure 1B. RI affected the PK of idarucizumab. The AUC_{0-24} and C_{max} of idarucizumab were increased by 38% and 20% in mild RI patients (CrCl 50 to <80 mL/min); 90% and 29% in moderate (CrCl 30 to <50 mL/min); and 146% and 33% in severe (CrCl <30 mL/min) RI patients when compared with patients with normal renal function (Table 1).

3.1.3 | By hepatic impairment

Hepatic impairment did not relevantly affect the PK of idarucizumab (Figure 1C).

3.1.4 | By region

There was no difference in the PK of idarucizumab between the patients from various geographic regions (Figure 1D).

3.2 | Total and unbound dabigatran

3.2.1 | Overall total and unbound dabigatran at baseline

There was a high interindividual variability for exposure of total dabigatran and corresponding unbound dabigatran (reflective of the variable disease states, renal function, dabigatran dose, and timing of the last dose of dabigatran before measurement). The median (range) concentrations were 139 (5.45-3600) ng/mL and 92.6 (1.0-2880) ng/mL, for total and unbound dabigatran, respectively. Among 21 patients whose baseline total dabigatran concentration was ≥1000 ng/mL, 15 patients had severe RI.

3.2.2 | By patient group

The concentrations of total and unbound dabigatran before idarucizumab treatment (baseline) did not differ between group A and group B patients. The total dabigatran levels were 165 ng/mL vs 110 ng/mL and unbound dabigatran levels were 103 ng/mL vs 69.5 ng/mL, in group A vs B, respectively (Table 2). In both patient groups, idarucizumab administration resulted in an immediate decrease in the concentration of unbound dabigatran to the lower limit of quantification; the gMean concentrations remained <20 ng/mL for the 24-hour observation period (Figure 2A).

3.2.3 | By renal impairment

At baseline, the plasma concentrations of total and unbound dabigatran were higher in patients with RI when compared with patients with normal renal function (Table 3). However, idarucizumab administration decreased the concentration of unbound dabigatran in patients with various degrees of RI; the gMean concentrations remained <20 ng/mL for the 24-hour observation period, except for the severe renal impairment group in which a slight increase above 20 ng/mL was observed 24 hours after idarucizumab (Figure 2B).

3.2.4 | By hepatic impairment

Hepatic impairment (defined as ALT/AST 1 – <2 × ULN; 2 – <3 × ULN; ≥3 × ULN) did not relevantly alter the effect of idarucizumab administration on the PK of dabigatran (Figure 2C).

3.2.5 | By region

Idarucizumab administration resulted in an immediate decrease in the concentration of unbound dabigatran in patients, irrespective of region (Figure 2D).

3.2.6 | Correlation between plasma concentration of unbound dabigatran and coagulation parameters

The relationship between unbound dabigatran plasma concentration and the primary coagulation tests, dTT and ECT, was explored. A close linear correlation was observed for both markers in the concentration range up to ~700 ng/mL unbound dabigatran (Figure 3A, B).

TABLE 1 Pharmacokinetic parameters of idarucizumab following administration of idarucizumab in patients with renal impairment

Renal impairment	Normal (CrCl ≥80 mL/min)		Mild (CrCl 50 to <80 mL/min)		Moderate (CrCl 30 to <50 mL/min)		Severe (CrCl <30 mL/min)	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
AUC_{0-24}	76	47 100 (30.6)	116	65 000 (29.8)	96	89 700 (32.2)	59	116 000 (36.6)
C_{max}	89	20 700 (33.3)	136	24 900 (29.2)	109	26 700 (31.0)	77	27 500 (26.7)

Abbreviations: AUC_{0-24}, area under the concentration–time curve from 0 to 24 hours postdose; C_{max}, maximum plasma concentration; CrCl, creatinine clearance; gCV%, geometric coefficient of variation; gMean, geometric mean.

TABLE 2 Plasma concentrations of total and unbound dabigatran at baseline

	Total dabigatran (ng/mL)[a]		Unbound dabigatran (ng/mL)[b]	
	N	gMean (gCV%)	N	gMean (gCV%)
Group A	281	165 (157)	288	103 (216)
Group B	191	110 (145)	193	69.5 (180)
Groups A and B	472	140 (156)	481	87.8 (205)

Abbreviations: BLQ, below the limit of quantification; gCV%, geometric coefficient of variation; gMean, geometric mean.
[a]BLQ values not considered in descriptive statistics; eight patients had BLQ at baseline.
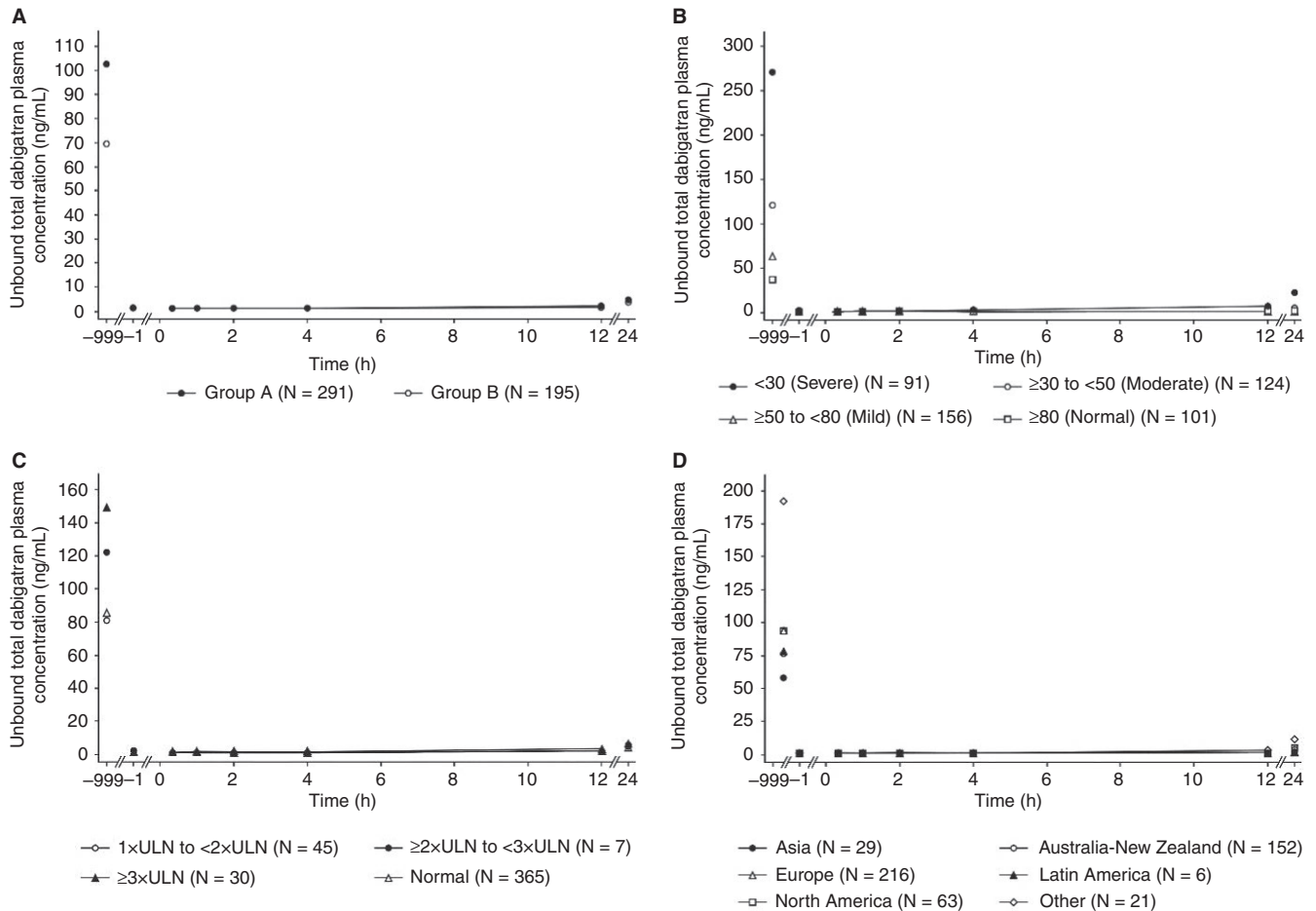[b]BLQ values replaced with 1.00 ng/mL.

FIGURE 2 Geometric mean plasma concentration–time profiles of unbound dabigatran following administration of idarucizumab 5 g in (A) patients from group A and group B; (B) patients who are renally impaired; (C) patients with hepatic impairment; and (D) in patients from different regions

3.2.7 | Timing and magnitude of recurrence of unbound dabigatran concentrations

The timing of recurrence appeared to depend upon baseline unbound dabigatran levels, with higher concentrations (≥1000 ng/mL) related to earlier recurrence. The magnitude of recurrence appeared to be associated with both elevated baseline unbound dabigatran concentrations and impaired renal function. Of 16 patients with recurrence up to 4 hours after idarucizumab treatment, all had higher baseline unbound dabigatran concentrations >640 ng/mL and 14 had CrCl <40 mL/min.

## 3.3 | Anti-idarucizumab antibodies

3.3.1 | Pre-existing ADAs

A total of 28 of 501 (5.6%) evaluable patients tested positive for ADAs against idarucizumab. Of these, 19 patients tested positive

TABLE 3 Plasma concentrations of total and unbound dabigatran at baseline by RI

Renal impairment	Normal (CrCl ≥80 mL/min)		Mild (CrCl 50 to <80 mL/min)		Moderate (CrCl 30 to <50 mL/min)		Severe (CrCl <30 mL/min)	
	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Total dabigatran (ng/mL)	93	72 (114)	154	99.8 (114)	124	177 (147)	87	381 (120)
Unbound dabigatran (ng/mL)	100	37.1 (204)	156	63.5 (137)	124	122 (159)	87	272 (135)

Abbreviations: CrCl, creatinine clearance; gCV%, geometric coefficient of variation; gMean, geometric mean.

A
Intercept = 32.04
Slope = 0.124
R^2 = 0.8765

B
Intercept = 43.588
Slope = 0.4935
R^2 = 0.8733
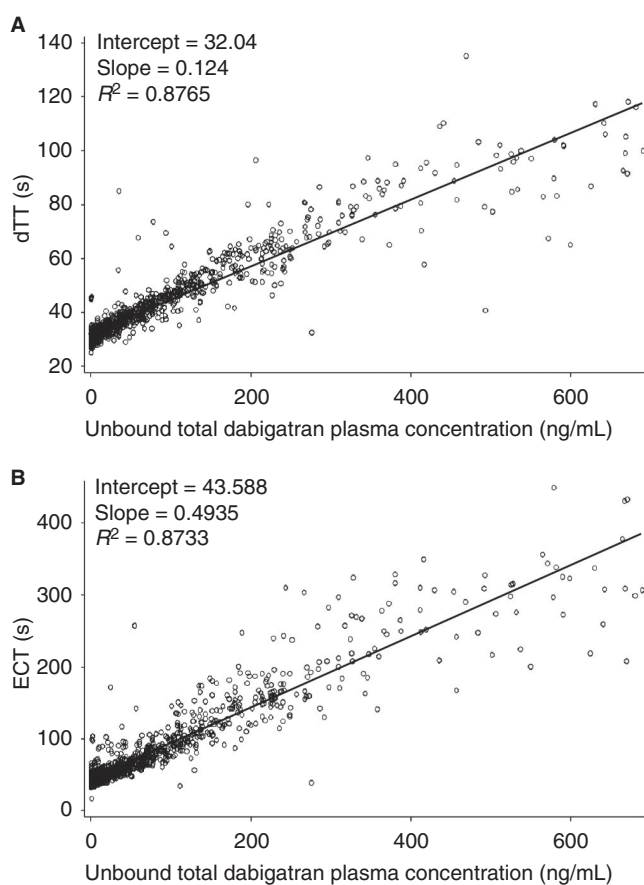
FIGURE 3 *Correlation between unbound dabigatran with (A) dTT and (B) ECT. dTT, diluted thrombin time; ECT, ecarin clotting time*

for ADAs before idarucizumab administration (pre-existing ADAs). Of these 19 patients, 16 showed the presence of ADAs during the follow-up period, indicating a possibly persistent response. The remaining three patients tested positive for ADAs before idarucizumab administration and/or at the 30-day follow-up, but tested negative at the 90-day follow-up, indicating a transient response (Table 4). For most cases (n = 17), ADAs were directed against the C-terminus epitope; for two patients, there was a switch or mixed specificity.

3.3.2 | Treatment-emergent ADAs

Nine of 501 patients (1.8%) had a treatment-emergent ADA response. The response was possibly persistent in eight patients and transient in one patient who tested positive only at the 30-day follow-up visit, but not at the 90-day visit (Table 5).

3.3.3 | Effect of ADAs on the PK/PD of idarucizumab

Anti-idarucizumab antibodies had no apparent effect on the PK or PD of idarucizumab; individual plasma concentrations of idarucizumab, dabigatran, and coagulation times of ADA-positive patients were generally within the 95th percentile of the overall population.

4 | DISCUSSION

The results of the present study are consistent with the idarucizumab PK in phase I and confirm that patient characteristics such as type (bleeding or surgical), geographic region, or presence of hepatic impairment have no impact on the PK of idarucizumab and its target dabigatran. Consistent with earlier findings, RI altered the PK of idarucizumab.[8] ADAs were detected in low frequency and low titers; however, these had no effect on the PK or PD of idarucizumab.[9]

The PK profile of idarucizumab showed a similar pattern in patients from both bleeding and surgical cohorts. The observed idarucizumab plasma concentration–time profiles were consistent with the findings in phase I studies of healthy volunteers, elderly volunteers, and volunteers with mild or moderate RI.[7,8]

Renal impairment was the major factor that had an effect on the PK of idarucizumab, whereby idarucizumab AUC increased with severity of RI. The effect was less pronounced for C_{max}, because C_{max} after a single intravenous infusion is not expected to be substantially affected by the clearance. These findings are consistent with the earlier observations from a phase I study in RI subjects.[8] An at least equimolar (1:1) amount of idarucizumab is needed for complete binding and reversal of dabigatran.[7,8] In RI, dabigatran exposure is increased because of increased half-life.[8,11] Consequently, the increase in idarucizumab exposure with RI may contribute to the complete reversal of the anticoagulant effects of dabigatran.[8]

Increased idarucizumab exposure was not associated with adverse safety signals, as demonstrated in outcomes from the RE-VERSE AD full cohort analysis.[6] This observation therefore

TABLE 4 Characterization of individual pre-existing ADAs observed in 19 of 501 subjects from the RE-VERSE AD Study, showing ADA titers and percentage blocking of ADAs by alternative molecules

Assay[a]	Assay response			Comments
	Baseline	**30-d**	**90-d**	
Group A				
ADA	4	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	6.3			Anti-C-terminus
Molecule 2	93.2			
ADA	64	64	16	Pre-existing, possibly persistent response
Molecule 1	13.8	8.8	−12.4	Anti-C-terminus
Molecule 2	89.8	98	96.9	
ADA	4	4	4	Pre-existing, possibly persistent response
Molecule 1	6	−0.2	14	Anti-C-terminus
Molecule 2	93.6	94.6	93.6	
ADA	8	1	1	Pre-existing, possibly persistent response
Molecule 1	−13.8	−22.9	−31.6	Anti-C-terminus
Molecule 2	93.7	90.5	90.6	
ADA	2	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	−24.7			Anti-C-terminus
Molecule 2	90.4			
ADA	2	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	25.6			Anti-C-terminus
Molecule 2	90			
ADA	8	0	0	Pre-existing, transient response
Molecule 1	−29.4			Anti-C-terminus
Molecule 2	93.3			
ADA	1	2	2	Pre-existing, possibly persistent response
Molecule 1	3.1	−22.4	20.8	Anti-C-terminus
Molecule 2	85.1	82.8	87.1	
Group B				
ADA	2	1	0	Pre-existing, transient response
Molecule 1	1.5	−14.9		Anti-C-terminus
Molecule 2	83.9	67.3		
ADA	8	2	Missing	Pre-existing, possibly persistent response
Molecule 1	7.2	10.6		Anti-C-terminus
Molecule 2	97	90.3		
ADA	4	4	4	Pre-existing, possibly persistent response
Molecule 1	33.5	6.2	33.6	Anti-C-terminus
Molecule 2	95	94.4	94.2	
ADA	4	4	Missing	Pre-existing, possibly persistent response
Molecule 1	−7.8	−11.9		Anti-C-terminus
Molecule 2	88.5	88		
ADA	2	1	1	Pre-existing, possibly persistent response
Molecule 1	8.8	−17.5	−60.2	Anti-C-terminus
Molecule 2	85.2	80.3	83.7	
ADA	8	4	8	Pre-existing, possibly persistent response
Molecule 1	8.6	−3	5.3	Anti-C-terminus

TABLE 4 (Continued)

Assay[a]	Assay response			Comments
	Baseline	30-d	90-d	
Molecule 2	86.7	85.4	87	
ADA	16	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	−10.4			Anti-C-terminus
Molecule 2	98.7			
ADA	4	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	5			Anti-C-terminus
Molecule 2	90.9			
ADA	2	Missing	Missing	Pre-existing, possibly persistent response
Molecule 1	32.6			Anti-C-terminus
Molecule 2	83.8			
ADA	4	2	2	Pre-existing, possibly persistent response
Molecule 1	4.2	−4.1	40.4	Anti-C-terminus
Molecule 2	91.8	87.1	87.3	
ADA	2	0	0	Pre-existing
Molecule 1	48			Mixed specificity
Molecule 2	80.1			

Abbreviations: ADA, anti-drug antibody assay (providing the titer); IgG, immunoglobin G.

[a]Titer, a titer in ADA assay (0 indicates an ADA-negative sample); molecule 1, assay for epitope specificity using the full length IgG version of idarucizumab (results are displayed as % inhibition of signal); molecule 2, a Fab with constant regions identical to idarucizumab but with different variable regions (results are displayed as % inhibition of signal).

supports the use of idarucizumab in the emergency setting. No dose adjustment of idarucizumab is recommended in RI.

Idarucizumab has not been studied in patients with hepatic impairment. Antibody fragments are known to be eliminated mainly by proteolytic catabolism in the kidney.[4] Therefore, an effect of hepatic impairment on the PK of idarucizumab was not expected, which was confirmed by the observations from the present study. The impact of ethnicity was not assessed; however, no relevant differences were observed when idarucizumab PK was analyzed by geographical region. Additionally, age has no effect on the PK of idarucizumab as indicated by a population PK analysis that included data from 220 volunteers and 486 patients (unpublished data). This is consistent with earlier findings in volunteers that observed no impact of age on the PK of idarucizumab.[8]

There was no difference in the levels of unbound dabigatran in bleeding (group A) and surgical (group B) patients. Dabigatran is primarily cleared via renal excretion.[11] Accordingly, dabigatran levels at baseline were increased in RI patients. RI had no effect on the reversal effects of idarucizumab.[6]

Overall, after idarucizumab administration, unbound dabigatran levels decreased to <20 ng/mL, a level that is presumed to produce little or no anticoagulant effect. The gMean concentrations remained <20 ng/mL during the observation period, indicating the almost complete binding of circulating dabigatran by idarucizumab. Nevertheless, a recurrence of unbound dabigatran concentrations of 20 ng/mL or higher was observed in 114 patients, most likely because of dabigatran being redistributed from the extravascular to the intravascular compartment. However, as reported previously,[6] only 10 patients with recurrent elevation in clotting time experienced bleeding. Consequently, a second dose of idarucizumab should only be considered in those patients with a recurrent elevation in clotting time who also have new-onset or recurrent bleeding. The magnitude of recurrence of unbound dabigatran concentrations was also associated with impaired renal function.

In the RE-VERSE AD trial, the median maximum percentage reversal of dabigatran was 100%, based on either the ECT or the dTT.[6] ECT and dTT are most suited for evaluating the anticoagulant activity of dabigatran and the reversal of dabigatran's effects by idarucizumab because of their close correlation with unbound dabigatran concentration.[7] We observed a linear correlation for both ECT (R^2 = 0.8733) and dTT (R^2 = 0.8765) with unbound dabigatran levels. Despite different coagulation assays with different sensitivities, and possible variation in the quality of patients' blood samples, the scatter of individual data points around the regression line did not generally impact the assessment of the extent of reversal in patients with the highest dabigatran levels. These findings were in line with phase I results.[7,8]

Our study extends observations on immunogenicity from phase I volunteer studies[9] to patients. Both pre-existing and treatment-emergent ADAs were observed in a smaller fraction of the target patient population compared with phase I volunteers—3.8% vs 11.7% and 1.8% vs 8.5%, respectively, for pre-existing and treatment-emergent ADAs. The reason for a lower ADA frequency in patients compared with volunteers was not immediately apparent. A decreased

TABLE 5 Characterization of individual treatment-emergent ADAs observed in 9 of 501 subjects from the RE-VERSE AD Study, showing ADA titers and percentage blocking of ADAs by alternative molecules

Assay[a]	Assay response			Comments
	Baseline	30-d	90-d	
ADA	0	1	1	Possibly persistent response
Molecule 1		−3.6	−15	
Molecule 2		80.2	79.8	Anti-C-terminus
ADA	0	8	8	Possibly persistent response
Molecule 1		92.1	94.6	
Molecule 2		56.8	51.9	Primarily antivariable
ADA	0	4	2	Possibly persistent response
Molecule 1		7.3	34.3	
Molecule 2		83.5	76.1	Anti-C-terminus
ADA	0	0	4	Possibly persistent response
Molecule 1			−0.7	
Molecule 2			84.1	Anti-C-terminus
ADA	0	8	0	Transient response
Molecule 1		50.2		Mixed specificity
Molecule 2		88.8		
ADA	0	4	Missing	Possibly persistent response
Molecule 1		19.9		Anti-C-terminus
Molecule 2		76.4		
ADA	0	0	4	Possibly persistent response
Molecule 1			94	
Molecule 2			52.4	Primarily antivariable
ADA	0	8	Missing	Possibly persistent response
Molecule 1		3.9		
Molecule 2		87.6		Anti-C-terminus
ADA	0	4	Missing	Possibly persistent response
Molecule 1		17.6		
Molecule 2		92.8		Anti-C-terminus

Abbreviations: ADA, antidrug antibodies; IgG, immunoglobulin G.
[a]Titer, a titer in ADA assay (0 indicates an ADA-negative sample); molecule 1, assay for epitope specificity using the full-length IgG version of idarucizumab (% signal inhibition); molecule 2, a Fab with constant regions identical to idarucizumab but with different variable regions (% signal inhibition).

immune response in the very elderly may account for this. The age of patients in this study (mean, 76.6 years; median, 78 years) was substantially higher compared with the volunteers in phase I (mean, 36 years; median, 32 years).[7,8,12] Overall, anti-idarucizumab ADAs were detected in a small fraction (5.6%) of the investigated patient population. The observed titers were extremely low relative to the idarucizumab dosage under evaluation, consistent with a pooled analysis of phase 1 trials,[9] and pre-existing ADAs had no apparent effect on the PK/PD of idarucizumab.

5 | CONCLUSIONS

Exposure to idarucizumab and its target dabigatran was increased in RI patients, whereas hepatic impairment and geographical region had no relevant effect on PK. Administering idarucizumab led to an immediate decrease in the concentration of unbound dabigatran to <20 ng/mL. There was a linear correlation between plasma concentration of unbound dabigatran and ECT and dTT assays. Pre-existing ADAs were detected in 3.8% of patients; most of these were C-terminus specific. Treatment-emergent ADAs were detected in 1.8% of patients. The observed titers of pre-existing and treatment-emergent ADAs were low and the presence of ADAs had no effect on the PK or PD of idarucizumab.

In the target patient population, the observed idarucizumab plasma concentration–time profiles, as well as its effects on dabigatran PK, were consistent with observations in phase I studies of healthy volunteers, the elderly, and volunteers with mild or moderate RI.

CONFLICT OF INTERESTS

The author(s) declared the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: S. Glund, K. Coble, D. Gansser, J. Stangier, K. Hoermann, and P. Reilly are employees of Boehringer Ingelheim. C.V. Pollack reports receiving consulting fees and research support from Boehringer Ingelheim, Janssen, and Portola; consulting fees only from BMS/Pfizer and CSL Behring; and research support from AstraZeneca.

AUTHOR CONTRIBUTION

S. Glund contributed to study design, data analysis, and manuscript development. K. Coble was responsible for the scientific oversight of the bioanalysis of the idarucizumab PK and ADA samples from this trial. D. Gansser was responsible for the scientific oversight of the bioanalysis of dabigatran PK samples from this trial. J. Stangier was responsible for the scientific oversight of the analysis of dabigatran PD samples

and evaluation of PD/PK analyses. K. Hoermann was involved in the evaluation of PK data from this trial. C.V. Pollack provided editorial input on the manuscript. P. Reilly contributed to the design and execution of the clinical trial and provided editorial input on the manuscript.

REFERENCES

1. Dager W, Hellwig T. Current knowledge on assessing the effects of and managing bleeding and urgent procedures with direct oral anticoagulants. Am J Health Syst Pharm. 2016;73(10 Suppl 2):S14–26.

2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893–962.

3. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JI, et al. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. J Thromb Haemost. 2016;14(3):623–7.

4. European Medicines Agency. Praxbind [idarucizumab], product information. http://wwwemaeuropaeu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003986/WC500197462pdf [Internet]. 2018. Available from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003986/WC500197462.pdf

5. Pollack CV Jr, Reilly PA, Bernstein R, Dubiel R, Eikelboom J, Glund S, et al. Design and rationale for RE-VERSE AD: a phase 3 study of idarucizumab, a specific reversal agent for dabigatran. Thromb Haemost. 2015;114(1):198–205.

6. Pollack CV Jr, Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for dabigatran reversal – full cohort analysis. N Engl J Med. 2017;377(5):431–41.

7. Glund S, Stangier J, Schmohl M, Gansser D, Norris S, van Ryn J, et al. Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet. 2015;386(9994):680–90.

8. Glund S, Stangier J, van Ryn J, Schmohl M, Moschetti V, Haazen W, et al. Effect of age and renal function on idarucizumab pharmacokinetics and idarucizumab-mediated reversal of dabigatran anticoagulant activity in a randomized, double-blind, crossover phase Ib study. Clin Pharmacokinet. 2017;56(1):41–54.

9. Norris S, Ramael S, Ikushima I, Haazen W, Harada A, Moschetti V, et al. Evaluation of the immunogenicity of the dabigatran reversal agent idarucizumab during phase I studies. Br J Clin Pharmacol. 2017;83(8):1815–25.

10. Stangier J, Feuring M. Using the HEMOCLOT direct thrombin inhibitor assay to determine plasma concentrations of dabigatran. Blood Coagul Fibrinolysis. 2012;23(2):138–43.

11. Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49(4):259–68.

12. Yasaka M, Ikushima I, Harada A, Imazu S, Taniguchi A, Norris S, et al. Safety, pharmacokinetics and pharmacodynamics of idarucizumab, a specific dabigatran reversal agent in healthy Japanese volunteers: a randomized study. Research and Practice in Thrombosis and Haemostasis. 2017;1(2):202–15.