Design and rationale for RE-VERSE AD: A phase 3 study of idarucizumab, a specific reversal agent for dabigatran

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Summary
Idarucizumab, a Fab fragment directed against dabigatran, produced rapid and complete reversal of the anticoagulation effect of dabigatran in animals and in healthy volunteers. The Study of the REVERSAl Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD™) is a global phase 3 prospective cohort study aimed at investigating idarucizumab in dabigatran-treated patients who present with uncontrollable or life-threatening bleeding, and in those requiring urgent surgery or intervention. We describe the rationale for, and design of the trial (clinicaltrials.gov NCT02104947).

Background
Dabigatran is an oral thrombin inhibitor licensed for reduction of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF), treatment of venous thromboembolism (VTE) and, in more than 100 countries, for thromboprophylaxis after elective hip or knee replacement surgery. In phase 3 trials in AF and VTE treatment, which were conducted without a specific reversal agent, dabigatran was at least as effective as warfarin, but produced less serious bleeding. In particular, the risk of intracranial bleeding was significantly lower with dabigatran than with warfarin, although there was a higher risk of gastrointestinal bleeding with dabigatran at the 150 mg twice daily dose (1–5). Despite the lack of a reversal agent for dabigatran, mortality in patients with intracranial bleeds or major bleeds in extracranial sites was no higher with dabigatran than with warfarin. The effectiveness and safety of dabigatran observed in the clinical trials have been confirmed in several observational studies, including a recently published independent analysis of data from over 134,000 Medicare patients conducted by the United States Food and Drug Administration (FDA) (6–8). Nonetheless, as with all anticoagulants, life-threatening bleeding can occur with dabigatran. Although such bleeding is often multi-factorial in origin and may require various interventions, rapid reversal of the anticoagulant activity of dabigatran would eliminate the contribution of excess anticoagulation to the problem. Likewise, rapid reversal would also streamline management of dabigatran-treated patients who require urgent surgery or interventions. Therefore, a specific reversal agent for dabigatran would be desirable.

Idarucizumab is a humanised mouse monoclonal antibody fragment directed against dabigatran, the active moiety of dabigatran etexilate. The affinity of idarucizumab for dabigatran is more than 300-fold higher than the affinity of dabigatran for thrombin (11, 12). Consequently, in sufficient doses, idarucizumab binds both free and thrombin-bound dabigatran, and the idarucizumab-dabigatran complex is then cleared by the kidneys. Idarucizumab is specific for dabigatran and because it is a Fab fragment, it does not bind to Fc receptors, and has no known endogenous targets (Figure 1) (11, 12). In preclinical studies, idarucizumab rapidly reversed the anticoagulant effects of dabigatran and attenuated dabigatran-induced bleeding in various animal models, while showing no evidence of thrombogenicity (13, 14).

The key phase 1 findings with idarucizumab are summarised in Table 1. When healthy young volunteers were given 220 mg twice daily of dabigatran etexilate, idarucizumab rapidly and completely reversed the anticoagulant effect of dabigatran as measured using several coagulation markers including the diluted thrombin time (dTT), ecarin clotting time (ECT), and activated partial thromboplastin time (aPTT) and did not promote thrombin generation (15). Likewise, when healthy middle-aged or elderly
volunteers, or volunteers with mild or moderate renal impairment (creatinine clearances between 60 and 89 and 30 and 59 ml/minute [min], respectively) were given 220 mg (healthy) or 150 mg (renal impairment) of dabigatran etexilate twice daily, idarucizumab also reversed its anticoagulant effects (16). When volunteers were re-started on dabigatran 24 hours (h) after idarucizumab administration, anticoagulation was restored, and was again reversed when a second dose of idarucizumab was given two months later (16). No drug-related adverse events were noted with idarucizumab and the only side effect was a transient, dose-related increase in urinary protein levels due to competitive inhibition of renal tubular re-uptake processes by the antigen-antibody complexes (16). Therefore, idarucizumab represents a promising reversal agent for dabigatran.

Recognising the unmet medical need for reversal agents for the non-vitamin K antagonist oral anticoagulants (NOACs), the FDA

Table 1: Key clinical phase I findings with idarucizumab in healthy volunteers (15, 16).

<table>
<thead>
<tr>
<th>Objective</th>
<th>Number of subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversal of anticoagulant effect of dabigatran in healthy young (age 18–64 years) volunteers</td>
<td>59</td>
<td>Dose dependent decrease in ECT, dTT, aPTT, TT and ACT</td>
</tr>
<tr>
<td>Reversal of anticoagulant effect of dabigatran in elderly (age 65–80 years) volunteers</td>
<td>16</td>
<td>Dose dependent decrease in ECT, dTT, aPTT, TT and ACT</td>
</tr>
<tr>
<td>Reversal of anticoagulant effect of dabigatran in subjects with creatinine clearance 44–79 ml/min</td>
<td>18</td>
<td>Dose dependent decrease in ECT, dTT, aPTT, TT and ACT</td>
</tr>
<tr>
<td>Pharmacokinetics of idarucizumab alone in healthy volunteers</td>
<td>110</td>
<td>Initial t1/2 ~45 min</td>
</tr>
<tr>
<td>Pharmacokinetics of dabigatran in volunteers given idarucizumab</td>
<td>93</td>
<td>Unbound dabigatran concentrations determined using HPLC/MS parallel results of clotting tests</td>
</tr>
<tr>
<td>Re-initiation of dabigatran 24 h after idarucizumab administration</td>
<td>12</td>
<td>Full anticoagulant effect of dabigatran 24 h after idarucizumab administration</td>
</tr>
<tr>
<td>Re-exposure to idarucizumab 2 months after initial administration</td>
<td>6</td>
<td>No hypersensitivity, 1 subject developed new anti-drug antibodies</td>
</tr>
<tr>
<td>Evaluation of potential procoagulant activity of idarucizumab</td>
<td>104</td>
<td>No increase in thrombin generation compared with placebo</td>
</tr>
<tr>
<td>Safety of idarucizumab</td>
<td>203</td>
<td>No dose-related adverse events, no serious adverse events</td>
</tr>
</tbody>
</table>
has granted idarucizumab and reversal agents for the oral factor Xa breakthrough therapy designation (17). Because there is no current standard of care for reversal of the NOACs, and because it would be unethical to withhold a reversal agent from a patient who may benefit from it, regulatory agencies recognised that randomised, placebo controlled trials are not possible. Instead, regulators have agreed that cohort studies are the only feasible approach for evaluating the safety of the reversal agents and to determine their capacity to reverse the anticoagulant effects of the target NOAC.

The study of the REVERSAd Effects of Idarucizumab in Patients on Active Dabigatran (RE-VERSE AD™) is one such study. RE-VERSE AD™ (NCT02104947) is a global phase 3 prospective cohort study aimed at investigating idarucizumab in dabigatan-treated patients who present with uncontrollable or life-threatening bleeding, and in those requiring urgent surgery or intervention. The primary endpoint of the study is the extent of reversal of the anticoagulant effects of dabigatran.

Study objectives and hypothesis

The primary objective of the study is to demonstrate the extent of reversal of the anticoagulant effect of dabigatran in patients who have uncontrolled or life-threatening bleeding, and in those requiring emergency surgery or other invasive procedures for which normal haemostasis is desirable. Secondary objectives include the reduction or cessation of bleeding, and evaluation of overall clinical outcomes, safety, and the pharmacokinetics of idarucizumab and of dabigatran in the presence of idarucizumab (Table 2). There will be a 90-day follow-up, at which time blood will be collected to test for antibodies against idarucizumab. The overall objective of the study is to show that idarucizumab administration to dabigatran-treated patients with a clinically determined need for reversal of anticoagulation will result in prompt, specific, and safe elimination of the anticoagulant effects of dabigatran as determined by central laboratory measurements of the ECT and dTT.

Study design and oversight

RE-VERSE AD is a multicentre, prospective, single arm observational study evaluating the effect of 5 g of intravenous idarucizumab in dabigatan-treated patients who present with uncontrollable or life-threatening bleeding, or in those requiring urgent surgery or intervention. The study sponsor is Boehringer Ingelheim (Ingelheim, Germany). The Steering Committee, which is comprised of academic and sponsor members, has final responsibility for the design of the trial, the development of the protocol, and oversight of the study. The protocol will be approved by the institutional review board or ethics committee of each of the more than 400 participating centres. Written informed consent is obtained from all patients or if the patient is unable to provide consent, from an acceptable patient representative where allowed by local laws. An independent Endpoint Adjudication Committee evaluates all suspected thrombotic events that occur within 90 days of idarucizumab administration, including strokes and systemic non-central nervous system embolic events, VTE events, myocardial infarctions, and deaths, as well as any other serious adverse event judged to be relevant. An independent Data Monitoring Committee periodically reviews the study outcomes and provides recommendations to the Steering Committee.

Patients

Two distinct groups of patients are eligible for inclusion in RE-VERSE AD. Group A patients are those who are taking dabigatran, are at least 18 years of age, have provided informed consent, and have overt bleeding that is judged by the treating clinician to require a reversal agent. Group B patients are those who are taking dabigatran, are at least 18 years of age, have provided informed consent, and have a condition requiring emergency surgery or invasive procedure where adequate haemostasis is required. Emergency surgery or invasive procedure is defined as a procedure that cannot be delayed for a minimum of 8 h. Exclusion criteria in Group A include the absence of clinical signs of active major bleeding or haemodynamic instability, or the presence of only minor bleeding (e.g. epistaxis, haematuria) that can be managed with standard supportive care. Exclusion criteria in Group B include index procedures that are elective or for which the risk of uncontrolled or unmanageable bleeding is low. In both groups, an additional exclusion criterion is any contraindication to study medication, including known hypersensitivity to idarucizumab or to the sorbitol excipient, such as hereditary fructose intolerance, which may lead to an adverse reaction. The inclusion and exclusion criteria were designed to allow the treating clinician to make the decision whether or not immediate reversal of the anticoagulant effect of dabigatran is warranted at the bedside.

Intervention

All patients receive 5 g of Idarucizumab as two 50 ml vials, each containing 2.5 g. The vials are given as an intravenous bolus infusion no more than 15 min apart, with the requirement for blood sampling in between. A fixed dose was selected to allow for simple administration without the need for measuring the extent of anticoagulation; no additional or partial doses are allowed. A total dose of 5 g was selected to reverse the anticoagulant effects of dabigatran in almost all patients based on dabigatran plasma concentrations measured in the RE-LY trial (18).

Outcome measures

Laboratory

The primary endpoint in both groups of patients is the maximum extent of reversal of the anticoagulant effect of dabigatran based on central laboratory determination of the dTT or ECT at any time point from the end of the first infusion up to 4 h after completion of the second infusion (Table 2). The 4 h time point was chosen because, based on phase I data, the maximum effect of...
Table 2: Complete listing of secondary objectives and safety endpoints of RE-VERSE AD study.

- Time to cessation of bleeding (for Group A only) since first infusion up to 24 h after the completion of second infusion. Bleeding status will be categorised before and at several time points after treatment.
- Occurrence of major bleeding (for Group B only) intraoperatively and up to 24 h post-surgery.
- Minimum unbound sum (free) dabigatran concentrations at any time point since end of first infusion up to 4 h after the completion of the last infusion.
- Duration of reversal, defined as the time period a patient remains completely reversed based on dTT or ECT, up to 24 h or re-starting the treatment of dabigatran.
- Reversal of anticoagulation as measured by dTT or ECT after the first infusion and before the start of the second infusion.
- Reversal of anticoagulation as measured by aPTT and TT, at any time point since the end of first infusion up to 4 h after the completion of the last infusion.
- Mortality.
- Number of days hospitalised, number of days in ICU (Intensive Care Unit).
- For ICH patients with serial CT scans, an estimate of blood volume.
- Normalisation of dTT and ECT, defined as a value of the coagulation test corresponding to a dabigatran plasma concentration (unbound sum) of 20 ng/ml (determined from a regression of dTT and unbound sum dabigatran from 1321.1 and 1321.2) or less, at any time since end of first infusion up to 4 h after the completion of the second infusion.
- Time to achieve complete reversal (100%) of anticoagulation based on dTT and ECT, since the end of first infusion.
- Time to achieve at least 80% reversal and 50% reversal of anticoagulation based on dTT and ECT, since the end of first infusion.
- Local laboratory assessment of dabigatran anticoagulant activity as determined by changes in aPTT.
- Reversal of anticoagulation as measured by dTT and ECT, from baseline to any time point since end of first infusion up to 30 min after the completion of the second infusion.
- Reversal of ACT at any time point since end of first infusion up to 4 h after the completion of the second infusion (applies only to patients in the cardiac catheterisation lab, where ACT is used as a determinant of level of anticoagulation).

For Group A (bleeding patients):

- Use of blood products after administration of idarucizumab (includes FFP, packed RBCs, platelets, volume expanders, tranexamic acid, cryoprecipitate, PCCs, Factor VIIa and any other haemostatic agents. Amount and time of administration will be recorded.
- Use of dialysis.
- Change from baseline in haematocrit, haemoglobin.
- Re-start of treatment with dabigatran or other anticoagulant.

For Group B (patients undergoing interventional procedures):

- Occurrence of bleeding. Bleeding will be categorised by the treating clinician as: normal haemostasis during the procedure; mildly abnormal intraprocedural haemostasis as judged by quantity or quality of blood loss (e.g. slight oozing); moderate abnormality in intraprocedural haemostasis (e.g. controllable bleeding); and severe haemostatic abnormality during the procedure (e.g. severe refractory haemorrhage).
- Re-start of treatment with dabigatran or other anticoagulant.

Safety assessment will include:

- Adverse events including local tolerability.
- Serious adverse events.
- Adverse reactions (adverse events related to treatment).
- Immune reactions assessed by adverse event collection.
- Formation of anti-drug antibodies.
- Clinically relevant changes in laboratory parameters, including renal and hepatic function.
- Blood pressure and heart rate hourly while in emergency department and every 4 h for the next 72 h.
- Thrombotic events (ischaemic stroke, myocardial infarction, pulmonary embolism, deep venous thrombosis, systemic embolism).
idarucizumab was expected to be rapid and because even in the absence of idarucizumab, dabigatran would be cleared with longer observation times in patients with normal renal function. Reversal of the anticoagulant effect will be characterised in terms of the mean time to maximum reversal, and the duration of reversal. The proportions of patients achieving at least 100%, 80% and 50% reversal will also be calculated. Maximum reversal of the anticoagulant effect of dabigatran is defined as

\[
\text{Reversal} = \frac{\text{predose coagulation test result (sec)} - \text{minimum postdose coagulation test result (sec)}}{\text{predose coagulation test result (sec)}} \times 100\%.
\]

Values equal to or higher than 100% will be interpreted as complete reversal of the anticoagulant effect. In addition to dTT and ECT, the central laboratory will also measure the thrombin time (TT) and aPTT (19, 20). The upper limit of normal (ULN) for each coagulation assay, which was determined using data from the phase I studies with idarucizumab, is the arithmetic mean + 2*SD using results collected prior to the dosing of dabigatran and the data from subjects who were on placebo as well as pre-dose data from idarucizumab alone treatment (as available), with SD denoting the standard deviation. A level of 110% ULN was chosen as the baseline for the normal anticoagulant effect because of the expected greater variability in the test results in patients in the RE-VERSE AD study compared with those of the healthy volunteers enrolled in the phase I studies. However, results will also be analysed using 100% ULN as the baseline.

In addition to coagulation assays, plasma concentrations of dabigatran will also be measured by high performance liquid chromatography-tandem mass spectroscopy (21). Both total and unbound sum dabigatran will be determined. Unbound sum dabigatran includes free dabigatran and its pharmacologically active glucuronide metabolites. Idarucizumab plasma concentrations will be assayed using an enzyme immunoassay developed by Covance Labs in Chantilly (VA, USA).

The tests used to demonstrate reversal will be performed in a central laboratory. The investigator will make clinical decisions based only on the clinical status of the patient and the results of local tests, such as the aPTT, TT or activated clotting time (ACT), and creatinine clearance. Local laboratory based aPTT assessment of reversal will ultimately be compared with the central laboratory assessments. The dose of idarucizumab is fixed and will not be influenced by local laboratory test results. The investigator may or may not see rapid resolution of bleeding, or adequate control of bleeding during surgery, depending on the patient and the factors contributing to the bleed. Selection of patients, the dose of antidote and the management of the patients are not dependent on measurements of dabigatran reversal.

Clinical

For patients who are bleeding (Group A), investigators will record the measures used to control bleeding and the sequence in which they are applied. These measures may be supportive (e.g. intravenous fluid resuscitation and transfusion), or may include physiological measures (e.g. cavity packing, cautery via endoscopy, embolisation under imaging guidance, or surgical), decontamination procedures (e.g. activated charcoal, gastric lavage, or haemodialysis), factor repletion (e.g. prothrombin complex concentrate [PCC], fresh frozen plasma [FFP], or activated recombinant factor VII), or administration of other haemostatic agents (such as tranexamic acid). The choice and sequence of these interventions are at the discretion of the treating clinician. In addition to documenting the volume of transfusion, the time to bleeding cessation will be recorded as will the time to haemodynamic stability in those who present with hypotension. For patients requiring urgent surgery or intervention (Group B), objective and real-time measures of blood loss will be recorded, as will any specific haemostatic measures, and the outcome of any neuraxial anaesthesia.

Clinical outcomes will be assessed in all patients. These are listed in Table 2 and include mortality, bleeding status and vital signs, which will be recorded at multiple time points after idarucizumab administration (10 min, 30 min, and 1 h, 2 h, 4 h, 12 h, and 24 h), length of stay in a critical care bed, and overall length of stay in hospital.

Surveillance and follow-up

After written informed consent is obtained, baseline blood collection for laboratory assessments will be performed, followed by intravenous administration of two 50 ml vials, each containing 2.5 g of idarucizumab. A blood sample is collected after administration of the first vial and then as per the schedule above after administration of the second vial. Severity of bleeding is assessed using the Glasgow Coma Score (GCS) and the Modified Rankin Scale (mRS) (25, 26). All patients will be evaluated for idarucizumab anti-drug antibodies at baseline, and at 30 and 90 days; ICH patients with intracranial haemorrhage (ICH) will also be assessed using the Glasgow Coma Score (GCS) and the Modified Rankin Scale (mRS) (25, 26). All patients will be evaluated for idarucizumab anti-drug antibodies at baseline, and at 30 and 90 days; ICH patients will undergo repeat mRS assessment at 90 days as well. For surgical patients, the surgeon will evaluate the extent of abnormal bleeding in the operative field (no abnormal haemostasis, mildly abnormal, moderately abnormal, and severely abnormal). Patients return at 7, 30 and 90 days for blood sample collection and/or for recording of any previously unreported clinical outcomes. The date of anticoagulation therapy initiation, and the drug used, will also be recorded.

Adverse event (AE) reporting

All AEs and serious AEs that occur during screening and up to 90 days after idarucizumab treatment will be recorded. An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment. A serious AE is defined as any AE which results in death, is not necessarily have to have a causal relationship with this treatment. A serious AE is defined as any AE which results in death, is
serious for any other reason if it is an important medical event when based upon appropriate medical judgment, and which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Event adjudication

All suspected thrombotic events occurring from the time of idarucizumab infusion to 90 days post-infusion will be adjudicated based on source documents and patient narratives. Stroke is defined as an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 h or more or resulting in death. The stroke will be categorised as ischaemic, haemorrhagic, or uncertain, based on CT or MRI or autopsy. Systemic embolism is an acute vascular occlusion of the extremities or any organ (e.g. kidney, spleen, or retina) and must be documented by angiography, surgery, scintigraphy, autopsy or other objective testing such as CT or MRI. For myocardial infarction (MI), among patients not undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), at least two of three criteria need to be met: a) severe chest pain or related symptoms or signs (e.g. ST- changes or T-wave inversions in the ECG) suggestive of MI, b) elevation of troponin or CK-MB to more than upper level of normal (ULN) or, if CK-MB was elevated at baseline, a re-elevation to more than a 50 % increase above the previous level, or c) development of significant Q-waves in at least two adjacent ECG leads. For patients undergoing PCI, MI is defined as elevation of troponin or CK-MB to more than 3 × ULN or if CK-MB was elevated at baseline, a re-elevation to more than 3 × ULN and more than 50 % increase above the previous level within 24 h of the procedure, and/or development of significant Q waves in at least two adjacent ECG leads. For patients undergoing CABG, MI is defined as elevation of CK-MB to more than 5 × ULN or, if CK-MB was elevated at baseline, a re-elevation to more than 5 × ULN and more than 50 % increase above the previous level within 72 h of the surgery, and/or development of significant Q-waves in at least two adjacent ECG leads. VTE, including deep venous thrombosis (DVT) and pulmonary embolism (PE), is defined by objective imaging studies such as compression ultrasound, ventilation/perfusion scan, CT pulmonary angiography, or autopsy. The severity of the index bleeding events (Group A) will be classified according to the above-mentioned scales, as will any abnormal surgical bleeding (Group B) designated as moderate or severe by the site surgeon. Deaths occurring within 90 days will be classified as vascular (including bleeding) or nonvascular, e.g. cancer, infection, trauma, respiratory failure. In addition to the adjudication of thrombotic events and death, measures of severity relating to the index presentation will be recorded and include presence of hypotension, acidosis, sepsis, disseminated intravascular coagulation, acute liver dysfunction, thrombocytopenia (platelet count less than 50,000/μl) or trauma.

Sample size

It is expected that approximately 200–300 patients will be entered into this trial. The sample size is based on practical considerations of the frequency of serious bleeding complications and emergency surgery in patients taking dabigatran, the recruitment rates, and the number of clinical trial sites that will be initiated. Based on the results of the RE-LY trial, life-threatening bleeding with the 150 mg dose occurs at a rate of approximately 1.5 events per 100 patient-years of treatment (1.5 %; 1.25 % with the 110 mg dose), while emergency surgery occurs at a rate of 1.5 %/year.

Statistical analysis

This trial has a single treatment group with no control group. It is a case series with a primary endpoint of reversal of anticoagulation effect determined by pharmacodynamic parameters. Since clotting tests may be influenced by factors other than dabigatran or idarucizumab, pharmacologically active dabigatran (unbound dabigatran) will also be quantified for independent verification of the coagulation test results (7). Although overall results will be presented, the two patient groups (bleeding patients and those requiring emergency surgery/procedures) will be analysed separately and together, with an overall conclusion achieved if possible. Assessment of efficacy will be based on descriptive statistics, with confidence limits provided when appropriate. As far as possible, the types of bleeding in the Group A cohort will be divided into subgroups based on presentation (e.g. ICH, trauma, gastrointestinal bleeds) and the clinical outcomes and biomarker endpoints will be analysed by subgroup. Analyses of correlations between the reversal effect and clinical outcomes will be undertaken for interim analyses and after completion of the trial.

An additional pre-specified cohort will be those patients enrolled by treating clinicians with the assumption that therapeutic anticoagulation by dabigatran was present, but for whom central laboratory analysis subsequently reveals subtherapeutic or no anticoagulation. These subjects will be included in the overall analysis but will also be presented as a pure safety population because they all will have been exposed to idarucizumab. All safety analyses will be descriptive in nature.

Discussion

RE-VERSE AD was designed to study the effectiveness and safety of idarucizumab for reversal of the anticoagulant effects of dabigatran in patients with uncontrollable or life-threatening bleeding or requiring urgent invasive procedures. A prospective case series approach was chosen instead of a randomised, controlled trial, because a) current strategies for the management of dabigatran-related bleeding vary from centre to centre, making the choice of a control approach difficult, b) comparison to PCC was not considered because the effect of PCC has yet to be systematically evaluated and cannot be considered standard care, and c) there are ethical concerns about denying patients with
life-threatening bleeding access to the only specific reversal agent (antidote) for dabigatran. This is in contrast to the previous studies evaluating warfarin reversal, where in addition to vitamin K, fresh frozen plasma and PCC are viable strategies and can therefore be directly compared. While improved clinical outcomes such as reduction or cessation of bleeding, or decreased bleeding-associated mortality in a controlled clinical trial would be preferred, ethical and logistic constraints, as well as the need for a large sample size, mean that such a trial would take many years to complete if it could be done at all. Even after over 50 years of vitamin K antagonist use, there is little evidence that vitamin K or factor repletion reduces mortality or improves clinical outcomes in patients with serious vitamin K antagonist-associated bleeds, such as ICH.

PCC has been shown to have variable effects on dabigatran-related bleeding in animal models and it fails to reverse the prolonged aPTT or to normalise the effects of dabigatran on thrombin generation (27, 28). In rabbits given dabigatran, PCC reduced blood loss and shortened the time to haemostasis after kidney injury compared with saline, but did not normalise the aPTT (27). In contrast to PCC, recombinant FVIIa had no effect (29). Although procoagulants, such as PCC, activated PCC and recombinant FVIIa, are often recommended in current guidelines (30-32), prospective clinical data on the utility of these agents for controlling dabigatran-related bleeding are lacking. For this reason, these agents could not be used as controls when evaluating the effectiveness of idarucizumab. Nonetheless, the RE-VERSE AD study does not preclude their use as prior or adjunct therapy. In fact, no other haemostatic measures are precluded in the study; idarucizumab can be used as first, only, or as add-on therapy in the clinical management of eligible subjects. Other management strategies include haemodynamic and haemostatic resuscitation and supportive measures (33), such as haemodialysis to remove dabigatran from the circulation (34), and the empiric use of other procoagulants (35, 36).

Demonstration of pharmacologic reversal of dabigatran anti-coagulation in the target patient population, coupled with data in the same patients showing that this reflects a decrease in unbound sum dabigatran levels was chosen as a reasonable endpoint for the clinical development of idarucizumab. The cohort of patients evaluated in this study will be heterogeneous in terms of their bleeding risk factors, source of bleeding or type of invasive procedure planned, comorbidities, and prognosis. Given the sample size of this study and the lack of a control group, the diversity of expected clinical outcomes precludes powering the study to evaluate them as a primary measure. Clinical outcomes will be tracked and reported, and to the extent that enrolment allows, similar patients (such as those with ICH) will be analysed and presented as specific cohorts.

Idarucizumab has no intrinsic procoagulant activity (12). Patients taking dabigatran, however, have prothrombotic disorders. Abrupt removal of the anticoagulant protection unmasks the underlying thrombotic risk and may lead to thrombotic complications, especially if there is a delay in re-instituting anticoagulation in vulnerable patients. Distinguishing between underlying risk and prothrombotic events may be difficult. PCC and other procoagulants have been associated with thrombotic complications, which may reflect increases in factor levels, the underlying disorder, or both (37-40). The study will provide robust safety information on idarucizumab because patients will be followed for both thrombotic complications and the development of anti-drug antibodies for 90 days.

The breakthrough therapy designation means that the FDA will work closely with the sponsor in evaluating the registration dossier as soon as it is filed (41). The study will continue until the target number of patients has been enrolled. Parallel programs evaluatingandexanet alfa (42), a reversal agent for factor Xa inhibitors, and aripazine (43), a synthetic cationic peptide that purportedly reverses both dabigatran and factor Xa inhibitors, are underway. It is likely therefore that there will soon be specific reversal agents for both dabigatran and the oral factor Xa inhibitors.

Conflicts of interest
Dr. Pollack reports receiving consulting fees from Boehringer Ingelheim, BMS/Pfizer, Daiichi-Sankyo, and Janssen, and research support from AstraZeneca. Drs. Reilly, Dubiel, and Wang are employees of Boehringer Ingelheim Pharmaceuticals. Drs. Glund, and Stangier are employees of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. Dr. Bernstein reports receiving consulting and research support fees from Boehringer Ingelheim, BMS/Pfizer, and Medtronic. Dr. Eikelboom reports receiving consulting fees from Boehringer-Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, and Janssen. Dr. Huisman reports receiving consulting fees from Boehringer Ingelheim. Dr. Hylek reports receiving consulting fees from Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Janssen, Medtronic, and Roche. Dr. Kam is an Honorary Medical Consultant to Boehringer Ingelheim. Dr. Kreuzer is an employee of Boehringer Ingelheim Pharma GmbH & Co. KG,Ingelheim, Germany. Dr. Kamphuisen reports receiving consulting fees from Boehringer Ingelheim, Daiichi-Sankyo, and Leopharma. Dr. Levy reports receiving consulting fees from Boehringer Ingelheim, Janssen, Portola, Roche, and The Medicines Company. Dr. Sellke reports receiving consulting fees from Boehringer Ingelheim. Dr. Steiner reports receiving consulting fees from Boehringer Ingelheim and is on a speaker bureau for Boehringer Ingelheim. Dr. Weitz reports receiving consulting fees from Boehringer Ingelheim, BMS, Pfizer, Bayer, Johnson & Johnson, Daiichi-Sankyo, Portola and ISIS Pharmaceuticals.

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