ADVANCING ANTICOAGULATION CARE: THE RE-VERSE AD™ CLINICAL STUDY

To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® (idarucizumab), a specifically targeted reversal agent to dabigatran etexilate, for use in rare emergency situations when patients require urgent reversal of its anticlotting effect.[1,2] The efficacy and safety of Praxbind® is now being evaluated in RE-VERSE AD™, an ongoing, global Phase III patient study in the emergency setting (NCT02104947).[2,3]

A Study of the **RE-VERS**al **E**ffects of Idarucizumab on **A**ctive **D**abigatran

RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran

MEDICAL NEED	• Although healthcare professionals are equipped with a range of clinical measures to manage bleeding complications, a specific reversal agent to dabigatran provides an important therapeutic addition for patient management in rare critical care situations when urgent reversal of the anticoagulant effect of dabigatran is required[2,4]
AIM	• RE-VERSE AD™ is designed to evaluate the safety and efficacy of Praxbind® for reversing the anticoagulant effect of dabigatran in real-world emergency situations, for example, in dabigatran-treated patients requiring an urgent procedure or emergency surgery (e.g. surgery for an open fracture after a fall) or dabigatran-treated patients with life-threatening or uncontrolled bleeding complications (e.g. intracranial haemorrhage or severe trauma after a car accident)[2]
STUDY DESIGN	• Global, multicentre, open-label, single-arm, Phase III study[2] • Designed to evaluate the types of patients and real-world situations healthcare professionals may see in the emergency setting – Broad inclusion criteria ensure that even severely ill or injured dabigatran-treated patients (e.g. patients with sepsis, a severe intracranial haemorrhage or a large vessel injury) who require urgent anticoagulant reversal may be enrolled[2]
PATIENTS	• Up to 500 dabigatran-treated patients will be enrolled from more than 400 centres in more than 35 countries worldwide[2,5,6] • Patients must be over 18 years of age and taking dabigatran, there are no upper age limits for entry[2]
TREATMENT AND FOLLOW-UP	• 5 g of intravenous Praxbind® administered as two 50 ml bolus infusions, each containing 2.5 g of Praxbind® no more than 15 minutes apart[2] • Administration of Praxbind® is dependent on medical history of dabigatran intake and healthcare professionals' judgement of the clinical situation and need for urgent anticoagulant reversal[2] • Blood coagulation levels will be evaluated:[2] – At baseline before the first infusion of Praxbind® – Just prior to the second infusion of Praxbind® – At multiple predefined time points after the second infusion • To ascertain the long term safety of Praxbind® adverse events will be monitored from the time of Praxbind® infusion up to 90 days post-infusion, including suspected thrombotic events or deaths (classified as vascular or non-vascular in origin)[2]
ENDPOINTS	• **Efficacy[2]:** – Primary: Degree of reversal of the anticoagulant effect of dabigatran, determined using different laboratory tests (including the coagulation tests diluted thrombin time [dTT] and ecarin clotting time [ECT]) at any point from the end of the first Praxbind® infusion, up to 4 hours after administration of the second infusion – Secondary: Secondary endpoints include the proportion of patients achieving complete normalisation of the dTT or ECT in 4 hours, the reduction in unbound dabigatran concentration, and clinical outcomes as assessed by the treating clinician • **Safety[2]:** Clinical outcomes including adverse events, formation of antibodies to Praxbind® (immunogenic reactions), patient status (e.g. blood pressure), incidence of thrombotic events (e.g. stroke/deep vein thrombosis/pulmonary embolism/myocardial infarction) and mortality

KEY DATES	**Start:** May 2014 **Estimated completion:** 2016[7]
RESULTS TO DATE	**Results from interim analyses of RE-VERSE AD™** Results from a first interim analysis including 90 patients enrolled in RE-VERSE AD™, simultaneously published in the *New England Journal of Medicine (NEJM)* and presented at the International Society of Thrombosis and Haemostasis 2015 Congress in Toronto, Canada in June 2015, demonstrated that:[8,9] • 5 g of Praxbind® immediately reversed the anticoagulant effect of dabigatran in patients requiring urgent anticoagulant reversal • After four and 12 hours, laboratory tests showed normal coagulation levels in almost 90 per cent of patients Updated results from data for 494 patients presented at the American Heart Association (AHA) Scientific Sessions 2016 in New Orleans, Louisiana showed:[10] • Praxbind® immediately reversed the anticoagulant effect of Pradaxa® in 100 percent of patients • For patients with extracranial bleeding, median time to confirmation of haemostasis was 3.5 to 4.5 hours, depending on anatomical location • For patients requiring emergency surgery or an invasive procedure, 93 percent of patients experienced normal haemostasis during surgery, and the median time to the operating room was 1.6 hours after administration of Praxbind® • No safety signals attributed to Praxbind® were detected. All serious adverse events reported were considered to be related to the index event or comorbidities rather than to study treatment • Thrombotic events occurred in 6.3 percent (31/494) of patients within 90 days after Praxbind® administration. Approximately two-thirds of these patients received no anticoagulation prior to the event • Mortality rates at 30 days were 12.3 percent in patients with uncontrolled or life-threatening bleeding and 12.4 percent in patients requiring emergency surgery or an invasive procedure, and 18.7 percent and 18.5 percent at 90 days respectively

References

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6. Pollack CV, *et al.* Idarucizumab for Reversal of the Anticoagulant Effects of Dabigatran in Patients in an Emergency Setting of Major Bleeding, Urgent Surgery, or Interventions. 1130M-05. Presented on Saturday 2 April 2016 at the American Congress of Cardiology 65th Annual Scientific Session & Expo, Chicago, USA.
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8. Pollack CV, *et al.* Idarucizumab for dabigatran reversal. *N Engl J Med.* 2015;**373**:511–20.
9. Pollack CV. Initial results of the RE-VERSE AD trial: idarucizumab reverses the anticoagulant effects of dabigatran in patients in an emergency setting of major bleeding, urgent surgery, or interventions. Oral presentation on Monday 22 June 2015 at the International Society of Thrombosis and Haemostasis 2015 Congress, Toronto, Canada.
10. Pollack C. V. *et al.* Idarucizumab for Dabigatran Reversal: Updated Results of the RE-VERSE AD Study. Oral presentation on 15 November 2016 at the American Heart Association (AHA) Scientific Sessions 2016, New Orleans, Louisiana, USA.