










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



To advance anticoagulation care, Boehringer Ingelheim developed Praxbind® (idarucizumab), a specific reversal agent to Pradaxa® (dabigatran etexilate). It was designed to reverse the anticoagulant effect of dabigatran in rare emergency situations.^{1,2} The efficacy and safety of Praxbind® has been evaluated in RE-VERSE AD™, a 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™ <small>Study of reversal effects of idarucizumab in patients on active dabigatran</small>
MEDICAL NEED 	<ul style="list-style-type: none"> Although healthcare professionals are equipped with a range of clinical measures to reduce bleeding risk and manage bleeding complications when they occur, a specific reversal agent to dabigatran provides an important therapeutic addition for patient management when urgent reversal of the anticoagulant effect of dabigatran is required in rare emergency situations.^{2,4} 	
AIM 	<ul style="list-style-type: none"> RE-VERSE AD™ has been designed to evaluate the safety and efficacy of Praxbind® for reversing the anticoagulant effect of Pradaxa® in emergency situations. These include the treatment of patients requiring an urgent procedure or emergency surgery (e.g. surgery for an open fracture after a fall) and the treatment of patients with life-threatening or uncontrolled bleeding (e.g. intracranial haemorrhage or gastrointestinal bleeding).² 	
STUDY DESIGN 	<ul style="list-style-type: none"> Global, multicentre, open-label, single-arm, Phase III study² The study was designed to reflect clinical practice in emergency management <ul style="list-style-type: none"> Broad inclusion criteria and minimal exclusion criteria ensured that even severely ill or injured patients (e.g. patients with sepsis, a severe intracranial haemorrhage or a large vessel injury) who required urgent reversal of the anticoagulant effects of Pradaxa® could be enrolled² There were no restrictions on use of other haemostatic agents in the study 	
PATIENTS 	<ul style="list-style-type: none"> A total of 503 dabigatran-treated patients were enrolled at 173 of a total 369 initiated sites in 39 countries worldwide^{2,5,6} Patients had to be taking dabigatran and be over 18 years of age; there were no upper age limits for entry² 	
TREATMENT AND FOLLOW-UP 	<ul style="list-style-type: none"> 5 g of intravenous Praxbind® administered as two 50 ml bolus infusions, each containing 2.5 g of Praxbind®, no more than 15 minutes apart² Administration of Praxbind® was dependent on healthcare professionals' judgement of the clinical situation and need for urgent anticoagulant reversal² Blood coagulation levels were evaluated:² <ul style="list-style-type: none"> 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 were 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 	<ul style="list-style-type: none"> Efficacy²: <ul style="list-style-type: none"> 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 included 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 Safety²: Clinical outcomes included 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 Completion: October 2016 ⁷
RESULTS TO DATE 	<p>Results from RE-VERSE AD™</p> <p>Results from a first interim analysis including 90 patients were presented at the International Society of Thrombosis and Haemostasis 2015 Congress in Toronto, Canada in June 2015 and simultaneously published in the <i>New England Journal of Medicine (NEJM)</i>.^{8,9}</p> <p>In July 2017, final data including 503 patients were presented as a late-breaking abstract at the International Society on Thrombosis and Haemostasis (ISTH) 26th Biennial Congress in Berlin, Germany and simultaneously published in the <i>NEJM</i>. The results confirmed the safety and efficacy of Praxbind® in emergency situations by validating that:^{10,11}</p> <ul style="list-style-type: none"> • Administration of Praxbind® resulted in immediate and complete reversal of the anticoagulant effect of Pradaxa® • Reversal was sustained for 24 hours in the majority of patients • In patients enrolled with acute bleeding for whom cessation of bleeding could be assessed, the median time to cessation of bleeding was 2.5 hours • In patients enrolled with a need for surgery or intervention, the required procedures could be initiated after a median of 1.6 hours • In 93.4 percent of patients requiring procedures, haemostasis during the procedure was described as 'normal' • No safety concerns attributed to Praxbind® were detected • Mortality rates at 90 days were 18.8 percent in patients admitted with uncontrolled bleeding and 18.9 percent in patients requiring urgent surgery • Thrombotic events at 90 days occurred in 6.3 percent of patients with uncontrolled bleeding and 7.4 percent of patients requiring urgent surgery, which is consistent with rates reported after major surgical procedures or hospitalisation for uncontrolled bleeding in patients who had taken a vitamin K antagonist.

References

1. Schiele F, *et al.* A specific antidote for dabigatran: functional and structural characterization. *Blood*. 2013;**121**:3554–62.
2. Pollack CV, *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**:198–205.
3. Boehringer Ingelheim Press Release, 22 May 2014. Antidote for rapid reversal of Pradaxa® (dabigatran etexilate) progresses into next stage of clinical investigation with study in patients. Available at <https://www.boehringer-ingelheim.com/press-release/antidote-rapid-reversal-pradaxa-dabigatran-etexilate-progresses-next-stage-clinical>. Last accessed: July 2017.
4. van Ryn J, *et al.* Dabigatran etexilate - a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost.* 2010;**103**:1116–27.
5. Pollack CV, *et al.* A Phase III Clinical Trial to Evaluate the Reversal Effects of Idarucizumab on Active Dabigatran (RE-VERSE AD™). Poster presentation at the International Stroke Conference, Nashville, USA, 11-13 February 2015.
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.
7. ClinicalTrials.gov. Reversal of Dabigatran Anticoagulant Effect With Idarucizumab. Available at: <https://clinicaltrials.gov/ct2/show/NCT02104947?term=idarucizumab&rank=1>. Last accessed: July 2017.
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 CV, Final results of the RE-VERSE AD study: Reversal of dabigatran by its specific reversal agent idarucizumab in patients with uncontrolled bleeding or requiring urgent surgery/procedures. Oral presentation on Tuesday 11 July 2017 at the International Society of Thrombosis and Haemostasis 2017 Congress, Berlin, Germany.
11. Pollack, C.V. *et al.* Idarucizumab for Dabigatran Reversal – Full Cohort Analysis. *N Engl J Med.* 2017; DOI: 10.1056/NEJMoa1707278. www.nejm.org/doi/full/10.1056/NEJMoa1707278.