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

Boehringer Ingelheim

To advance anticoagulation care, Boehringer Ingelheim developed 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 idarucizumab* is now being evaluated in RE-VERSE AD™, an ongoing, global Phase III patient study in the emergency setting (NCT02104947).[1,2]

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,[3] no specific reversal agent for any of non-vitamin K antagonist oral anticoagulants (NOACs) is currently approved[4]
- A specific reversal agent to dabigatran would provide an important therapeutic addition for patient management in rare critical care situations when urgent reversal of the anticoagulant effect of dabigatran is required[1]

AIM

- RE-VERSE AD™ will evaluate the safety and efficacy of idarucizumab* for reversing the anticoagulant effect of dabigatran in real-world emergency situations, for example, in dabigatran-treated patients requiring emergency surgery or an invasive procedure (e.g. surgery for an open fracture after a fall) or dabigatran-treated patients with uncontrolled or life-threatening bleeding complications (e.g. intracranial haemorrhage or severe trauma after a car accident)[1]

STUDY DESIGN

- Global, multi-centre, open-label, single-arm Phase III study[1]
- 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[1]

PATIENTS

- Up to 300 dabigatran-treated patients will be enrolled from more than 400 centres in 38 countries worldwide[1,5]
- Patients must be over 18 years of age and taking dabigatran - there are no upper age limits for entry[1]

TREATMENT & FOLLOW-UP

- 5 g of intravenous idarucizumab*, administered as two 50 ml bolus infusions, each containing 2.5 g of idarucizumab*, no more than 15 minutes apart[1]
- Administration of idarucizumab* is dependent on medical history of dabigatran intake and healthcare professionals' judgement of the clinical situation and need for urgent anticoagulant reversal[1]
- Blood coagulation levels will be evaluated:
  - At baseline before the first infusion of idarucizumab*
  - Just prior to the second infusion of idarucizumab*
  - At multiple predefined time points after the second infusion[1]
- To ascertain the long term safety of idarucizumab*, adverse events will be monitored from the time of idarucizumab* infusion to 90 days post-infusion including suspected thrombotic events or deaths (classified as vascular or non-vascular in origin)[1]

END-POINTS	• **Efficacy[1]:** o 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 idarucizumab* infusion, up to 4 hours after administration of the second infusion o 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[1]:** Clinical outcomes including adverse events, formation of antibodies to idarucizumab* (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:** 2017[6]

** Idarucizumab is the recommended International Nonpropriety Name (INN). Idarucizumab is an investigational drug, which has not yet been approved for clinical use, and further safety and efficacy testing will be required*

References

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2. Boehringer Ingelheim Press Release – 22 May 2015. Antidote for rapid reversal of Pradaxa® (dabigatran etexilate) progresses into next stage of clinical investigation with study in patients. Available at: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/22_may_2014_dabigatranetexilate.html.Last accessed June 2015.
3. 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.
4. Boehringer Ingelheim. Data on file.
5. Pollack C. V. *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. ClinicalTrials.gov. Reversal of Dabigatran Anticoagulant Effect With Idarucizumab. Available at: https://clinicaltrials.gov/ct2/show/NCT02104947?term=idarucizumab&rank=1.Last accessed June 2015.