Idarucizumab, a Specific Reversal Agent for Dabigatran: Immediate, Complete, and Sustained Reversal of Dabigatran Induced Anticoagulation Shown in Healthy and Renal Impaired Subjects

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BACKGROUND AND OBJECTIVE

The new oral anticoagulants are effective alternatives for warfarin, but specific reversal agents are not yet available for these drugs. Current options for management of bleeding patients requiring dabigatran treatment include: 1) interruption of treatment; 2) Supportive care; 3) Volume replacement/blood product transfusion/thrombin complex concentrate; 4) Hemodialysis. A specific reversal agent may provide an additional option for patient management during emergency situations.

Idarucizumab, a specific reversal agent for dabigatran, is in Phase II clinical testing (RE-VERSE AD™). A biological application has been submitted to the US Food and Drug Administration, and accelerated approval has been requested.

The objective of this study was to evaluate the safety, tolerability, and pharmacodynamics of idarucizumab after dabigatran-prolonged clotting time in male and female healthy middle-aged and elderly, or renally impaired volunteers.

Idarucizumab for Reversal of Dabigatran Induced Anticoagulation

Idarucizumab is a humanized antibody fragment (Fab). It binds dabigatran with high affinity, and off-rate binding is not expected.

Idarucizumab is being developed as a specific reversal agent to reverse the anticoagulant effect of dabigatran.

The key clinical characteristics of dabigatran are:

- Short half-life: initial half-life, ~45 minutes and terminal half-life, 4.5–9 hours
- Male and female volunteers with mild or moderate renal impairment (RI) who met the following criteria:
  - Age 45–64 years
  - BMI 16.5 to 30 kg/m²
- Healthy middle-aged volunteers (45–64 years) who received 5 g idarucizumab or corresponding placebo also received DE 24 hours later.
- Male and female volunteers with mild or moderate renal impairment (RI) who met the following criteria:
  - Creatinine clearance at screening: mild RI, 60 to < 90 mL/min; moderate RI, 30 to < 60 mL/min
- Aged 65–80 years (elderly) and BMI 18.5 to 32.0 kg/m².
- Male and female volunteers with mild or moderate renal impairment (RI) who met the following criteria:
  - Age 45–64 years
  - BMI 16.5 to 30 kg/m²

Study Population

- The study evaluated healthy male and female volunteers who met the following criteria:
  - Age 45–64 years (middle-aged and elderly group BMI 16.5 to 29.9 kg/m²)
  - Age 45–64 years (middle-aged and elderly group BMI 16.5 to 30.9 kg/m²)
- Male and female volunteers with mild or moderate renal impairment (RI) who met the following criteria:
  - Creatinine clearance at screening: mild RI, 60 to < 90 mL/min; moderate RI, 30 to < 60 mL/min
- Healthy middle-aged volunteers (45–64 years) who received 5 g idarucizumab or corresponding placebo also received DE 24 hours later.
- Male and female volunteers with mild or moderate renal impairment (RI) who met the following criteria:
  - Creatinine clearance at screening: mild RI, 60 to < 90 mL/min; moderate RI, 30 to < 60 mL/min

Study Design

- This was a Phase II, randomized, double-blind, placebo-controlled, four-way crossover study (NCT01918730).
- Treatments: 1:1 molar binding of idarucizumab to dabigatran was assumed.3

Methods

A 5-minute intravenous infusion of idarucizumab was administered in a single 1, 2.5, or 5 g dose, Healthy middle-aged or elderly volunteers and subjects with RI were randomized to intravenous administration of dabigatran (DE) 220 mg bid or in females and 150 mg bid and with mild or moderate RI received DE 150 mg bid for 3 days and 1 dose at the morning of day 4 (Figure 2).

Healthy middle-aged or elderly volunteers and subjects with RI were randomized to intravenous doses of idarucizumab or placebo in the presence of dabigatran.

A 1:1 molar dilution of dabigatran was administered in a single 25, 50, or 50 g dose, and 1 dose at 2:5 g over a 2-hour period (Figure 2).

Each subject received two treatment periods separated by 6-days of washout.

Healthy middle-aged (45–64 year) volunteers who received 2.5 g idarucizumab underwent re-exposure with 2.5 g idarucizumab approximately 2 months after the crossover period.

Healthy middle-aged volunteers (45–64 year) who received 5 g idarucizumab or corresponding placebo also received DE 24 hours later.

Adverse Events

- No AEs indicative of immunogenic reactions were observed.
- No AEs and local tolerability reactions were similar for placebo and active treatment.
- No relationship was observed between drug dose, sex, age, or renal function and frequency of AEs.
- A dose-dependent, transient increase in urinary protein and low-weight proteins was observed, but value returned to normal range within 6–44 hours.

RESULTS

- Median peak dabigatran exposure was comparable to exposure in patients with atrial fibrillation.
- Dabigatran therapy could be restarted 24 hours after idarucizumab.
- The dabigatran reversal agent, idarucizumab, was well tolerated under all conditions tested.
- Idarucizumab fulfills the requirements for a fast-acting and specific reversal agent to dabigatran with a favorable tolerability profile, a Phase IV clinical trial with dabigatran is ongoing.

CONCLUSIONS

- Administration of 5 g or 2 x 2.5 g idarucizumab led to complete and sustained reversal of dabigatran-induced anticoagulation in healthy middle-aged and elderly volunteers and subjects with renal impairment.
- Re-administration of idarucizumab 2 months later was effective and well tolerated.
- Dabigatran therapy could be restarted 24 hours after idarucizumab.

Endpoints

- The safety, tolerability, and intravenous safety of idarucizumab were assessed as primary endpoints.
- An additional primary endpoint was the median prolongation of international normalized ratio (INR) by dabigatran.
- Restoration of anticoagulation after re-exposure to DE 24 hours following dabigatran-induced anticoagulation was also evaluated.

Analyses

- Central analyses of dabigatran diluted thrombin time (dTT), aPTT clotting time (dTT), and thrombin time (TT): dTT was measured here, and APTT, TT, and PT were measured later.

Statistical Evaluation

- Safety outcomes and pharmacodynamic endpoints were evaluated descriptively.

References


Figure 1: Fragments antigens binding (Fab)

Figure 2: Study design

Figure 3: Reversal of dabigatran clotting time with idarucizumab

Figure 4: DE-re-exposure 24 hours after idarucizumab infusion

Figure 5: DE + placebo DE + Idarucizumab