Idarucizumab, a Specific Reversal Agent for dabigatran: Immediate, Complete, and Sustained Reversal of dabigatran Induced Anticoagulation Shown in Healthy Male Volunteers

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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 agents. Idarucizumab (BI 870007) is a monoclonal antibody that specific reverses the anticoagulant effects of dabigatran etexilate (DE) via a competitive mechanism. The study included Part I: Male volunteers (N = 110) were randomized (6:2) to receive single intravenous doses of idarucizumab of 1, 2, or 4 g (n = 30/30/30), or placebo (n = 30). Part II: Male volunteers (n = 35) were randomized (9:3) to receive idarucizumab intravenous infusions or placebo (n = 35) at a dose of 2 g (n = 10) or 4 g (n = 10), with DE 150 mg bid. DE 220 mg bid was administered in healthy male volunteers to achieve a normalized ratio (N.R.) of 1.25. The primary endpoint was the bleeding time at 0.5 hour after end of infusion.

Methods
Study population: All healthy male volunteers who met the following criteria: age 18–45 years; Body mass index 18.5 to 29.9 kg/m²; randomization list tape, randomization code, investigator list tape, investigator data, and investigator agreement to study protocol. Part I: Male volunteers (N = 110) were randomized (6:2) to receive single intravenous doses of idarucizumab of 1, 2, or 4 g (n = 30/30/30), or placebo (n = 30). Part II: Male volunteers (n = 35) were randomized (9:3) to receive idarucizumab intravenous infusions or placebo (n = 35) at a dose of 2 g (n = 10) or 4 g (n = 10), with DE 150 mg bid. DE 220 mg bid was administered in healthy male volunteers to achieve a normalized ratio (N.R.) of 1.25. The primary endpoint was the bleeding time at 0.5 hour after end of infusion. Safety analysis was based on the number (%), type, and severity of AEs.

Results
Safety: All AEs were considered related to idarucizumab. No hematological, biochemical, or clotting studies indicated evidence of a significant pharmacodynamic interaction with dabigatran. The mean clotting times were reversed to baseline immediately after the end of the idarucizumab infusion. Endogenous thrombin potential (ETP) was determined ex vivo by measuring the area under the thrombin peak curve (AUC). The measurement of ETP is an indicator of the magnitude of coagulation activation. Endogenous thrombin potential was determined ex vivo by measuring the area under the thrombin peak curve (AUC). The measurement of ETP is an indicator of the magnitude of coagulation activation. Endogenous thrombin potential was determined ex vivo by measuring the area under the thrombin peak curve (AUC).

Conclusions
Idarucizumab is a specific reversal agent for dabigatran. Idarucizumab resulted in immediate complete and sustained reversal of dabigatran induced anticoagulation shown in healthy male volunteers.

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