ANNEXA™-R Part 2: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial Demonstrating Sustained Reversal of Rivaroxaban-Induced Anticoagulation in Older Subjects by Andexanet Alfa (PRT064445), a Universal Antidote for Factor XA (FXA) Inhibitors

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Background: Direct FXa inhibitors have superior or comparable efficacy and safety relative to warfarin. A specific antidote for these agents is lacking in case of major bleeding or emergent surgery. Andexanet alfa (AnXa) is a modified, recombinant human FXa molecule under development as a specific antidote for FXa inhibitors. We have reported data for Part 1 of the Phase 3 study in older subjects anticoagulated with rivaroxaban, where an AnXa IV bolus reversed anti-FXa activity and restored thrombin generation (TG). Here we report Part 2 data where AnXa was administered as a bolus-plus-infusion (B+I) regimen in a similar population. Data from the phase 3 study in older subjects anticoagulated with apixaban has also been reported demonstrating rapid and sustained reversal of anti-FXa activity and restored TG with AnXa IV bolus or B+I.

Aims: To demonstrate immediate and sustained reversal of rivaroxaban anticoagulation following bolus and infusion of AnXa.

Methods: ANNEXATM is a 4 part, Phase 3, double-blind, placebo-controlled program comprised of 2 studies of AnXa in older subjects treated with rivaroxaban or apixaban. Part 2 investigated a bolus of AnXa plus a 2-hr infusion. In ANNEXA-R Part 2, 39 subjects age 50 to 75 were randomized to receive AnXa or placebo in a 2:1 ratio. All subjects received rivaroxaban 20 mg PO QD for 4 days to achieve steady state plasma levels. AnXa (800 mg IV bolus plus a 2-hr infusion at 8 mg/min) or placebo was administered on Day 4, 4 hrs after the last rivaroxaban dose (~Cmax). Safety data were collected through Day 43. The primary efficacy endpoint is the percent change from baseline in anti-Xa activity at its nadir between 10 min prior to and 5 min after end of infusion. Additional endpoints included reduction in plasma free fraction of rivaroxaban and restoration of TG.

Results: AnXa rapidly reversed the anticoagulant effect of rivaroxaban and sustained it for the duration of the infusion. AnXa was well tolerated.

Conclusion: This study continues our investigations of AnXa as an antidote for reversing the anticoagulant effects of rivaroxaban and other FXa inhibitors. Rapid and near complete reversal of the anti-Xa effect of the FXa inhibitors has the potential to improve management of patients with bleeding or those requiring emergent surgery.

Disclosure:
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