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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Disclosures

Presenter's Financial Disclosure

Consultant, Portola Pharmaceuticals

- Dr. Crowther discloses having sat on advisory boards for Janssen, Leo Pharma, Portola, and AKP America. Dr. Crowther holds a Career Investigator award from the Heart and Stroke Foundation of Ontario, and the Leo Pharma Chair in Thromboembolism Research at McMaster University. Dr. Crowther's institution has received funding for research projects from Leo Pharma. Dr. Crowther has received funding for presentations from Leo Pharma, Bayer, Celgene, Shire and CSL Behring.

Unlabeled/Unapproved Uses Disclosure

The use of andexanet alfa (PRT064445)* as an antidote for factor Xa inhibitors is investigational.

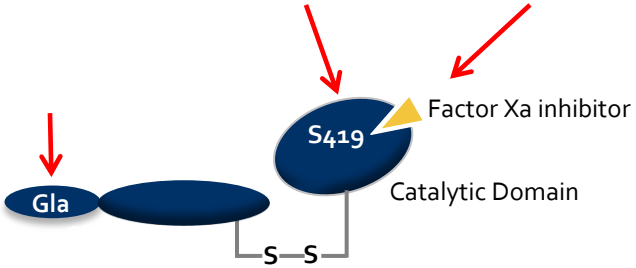
Portola Pharmaceuticals analyzed the data and participated in the preparation of this presentation.

*Andexanet alfa (AnXa) is the nonproprietary name of PRT064445

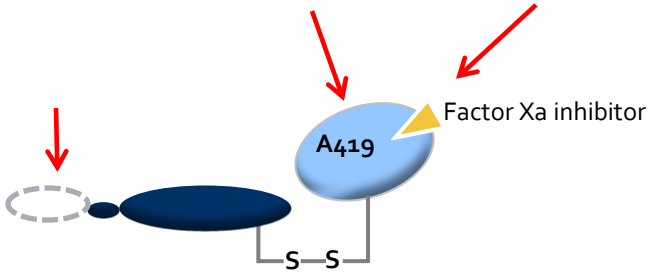
Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors
Nature Medicine (2013),19(4): 446-51

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all direct fXa inhibitors
- Change of serine to alanine to eliminate catalytic activity and prevent prothrombin cleavage
- GLA domain removed to prevent anticoagulant effect



Factor Xa



Andexanet Alfa

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)

- Retains high affinity for Antithrombin III-inhibitor complex and can reverse ATIII-dependent anticoagulant effects of enoxaparin and fondaparinux in vitro and in vivo

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Andexanet Has Demonstrated Deep and Rapid Reversal of Biomarkers of Anticoagulation for Four fXa Inhibitors to Date

- **Multiple Phase 2 Proof-of-Concept Studies**

  - ☑ Apixaban 5 mg PO Q12 – *completed; successful*
  - ☑ Rivaroxaban 20 mg PO QD - *completed; successful*
  - ☑ Enoxaparin 40 mg SQ QD – *completed; successful*
  - ☑ Edoxaban 60 mg PO QD – *completed; successful for cohorts analyzed to date*
  - ☐ Betrixaban 80 mg PO QD – *ongoing*

- **Phase 3 and Confirmatory Registration-enabling Studies**

  - ☑ Phase 3 studies: older healthy subjects treated with apixaban or rivaroxaban – *completed; successful*
  - ☑ Phase 4 "Confirmatory study" with bleeding patients – *ongoing*

Planning enrollment of bleeding patients with rivaroxaban, apixaban, edoxaban, and enoxaparin

ANNEXA™
Phase 3 Registration-enabling Studies

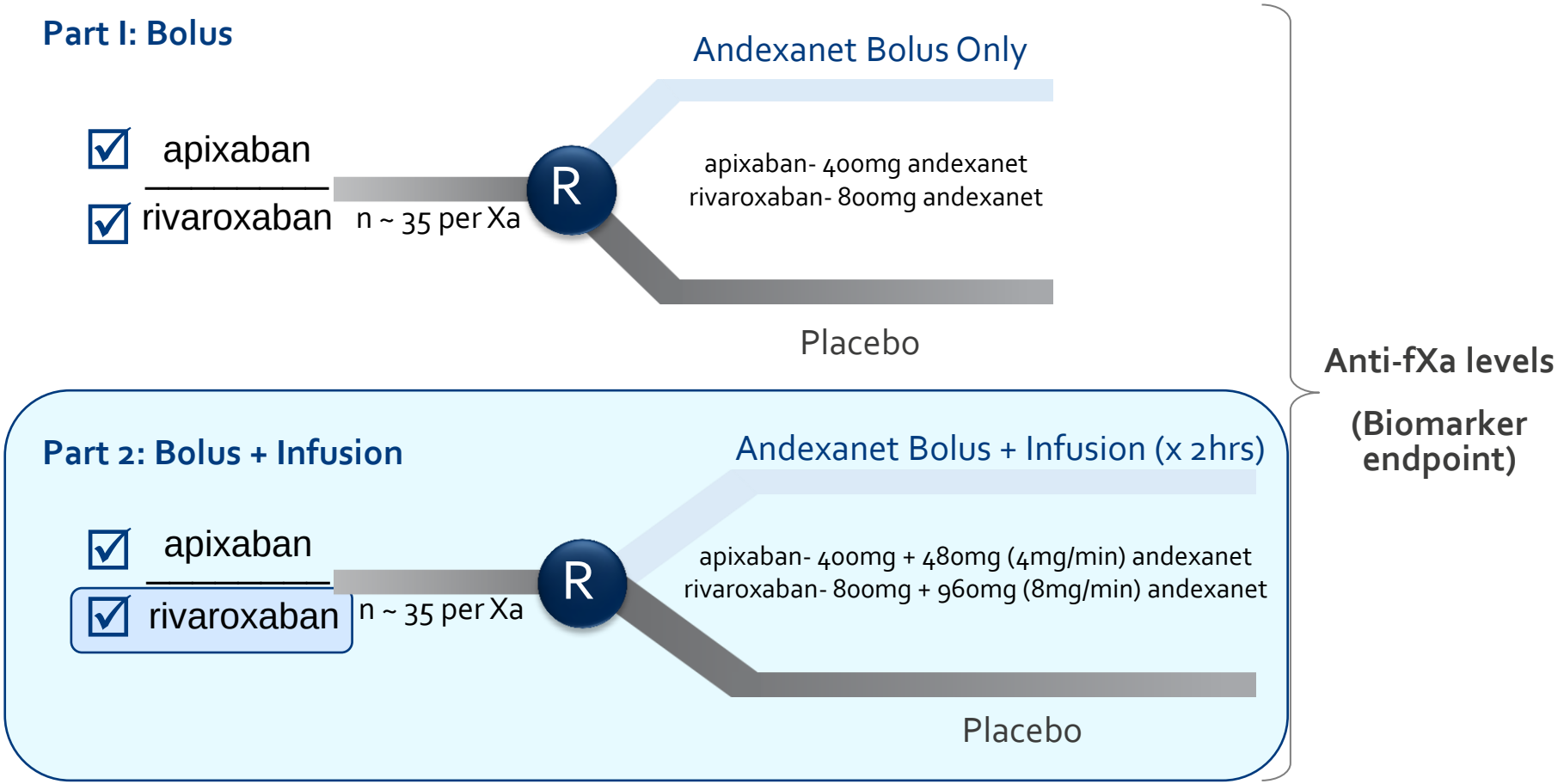
Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors

ANNEXA-A: Apixaban

ANNEXA-R: Rivaroxaban

Andexanet Alfa: ANNEXA™ Registration-Enabling Studies

Accelerated Approval Phase 3 Design for Apixaban and Rivaroxaban



R: Randomization

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ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Baseline Characteristics and Demographics

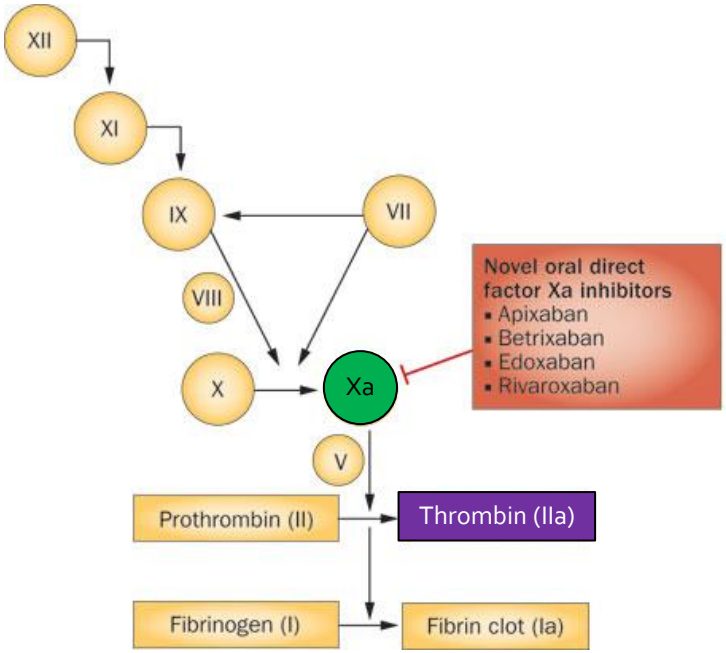
(Randomization: Andexanet:Placebo = 2:1)

	Placebo (N = 13)	Andexanet (N = 26)
Gender, n (%) Male	**6 (46.2%)**	**11 (42.3%)**
Age, years		
Mean	**58.1**	**57.0**
SD	**5.45**	**5.08**
Median	**57.0**	**56.0**
Min, Max	**52, 67**	**50, 68**
Race, n (%) White	**8 (61.5%)**	**20 (76.9%)**
Ethnicity, n (%) Hispanic or Latino	**4 (30.8%)**	**10 (38.5%)**

Rationale for Biomarker Endpoints

The primary endpoint should directly measure:

- The fXa activity and determines the degree to which andexanet reverses the inhibitory activity of the anticoagulant
- Anticoagulant activity using a well-established assay for fXa inhibitors
  - **Anti-fXa levels**
- Sequestration of the anticoagulant by andexanet
  - **Unbound fXa inhibitor concentration**
- Restoration of coagulation distal to fXa inhibition
  - **Thrombin generation**



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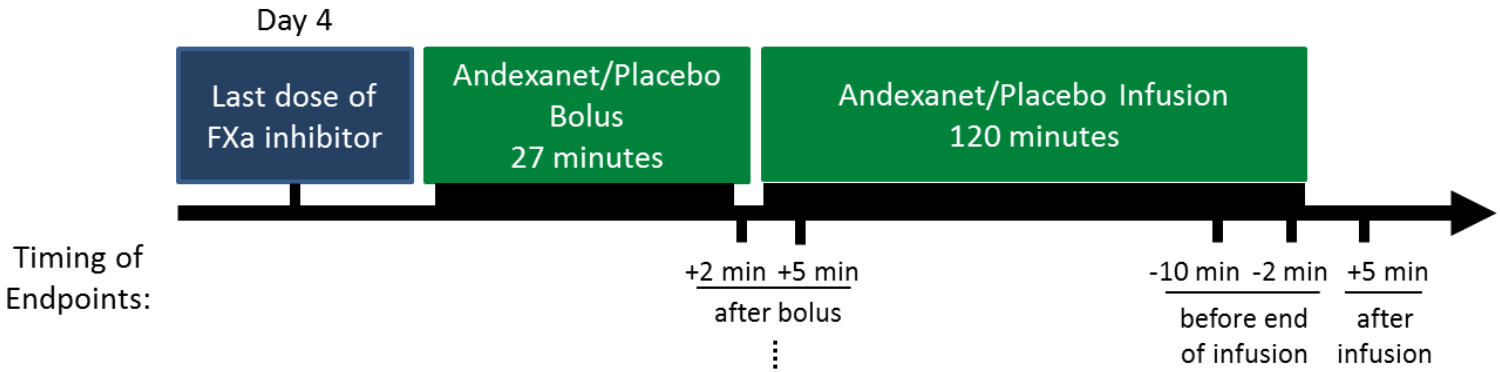
ANNEXA™-R (Rivaroxaban, Bolus + Infusion)



Primary Endpoint:

1. Percent change in anti-fXa activity

Secondary Endpoints:

1. Percent change in anti-fXa activity
2. Occurrence of 80% or greater reduction in anti-fXa activity
3. Change in free rivaroxaban concentration
4. Change in thrombin generation
5. Occurrence of thrombin generation above lower limit of derived normal range

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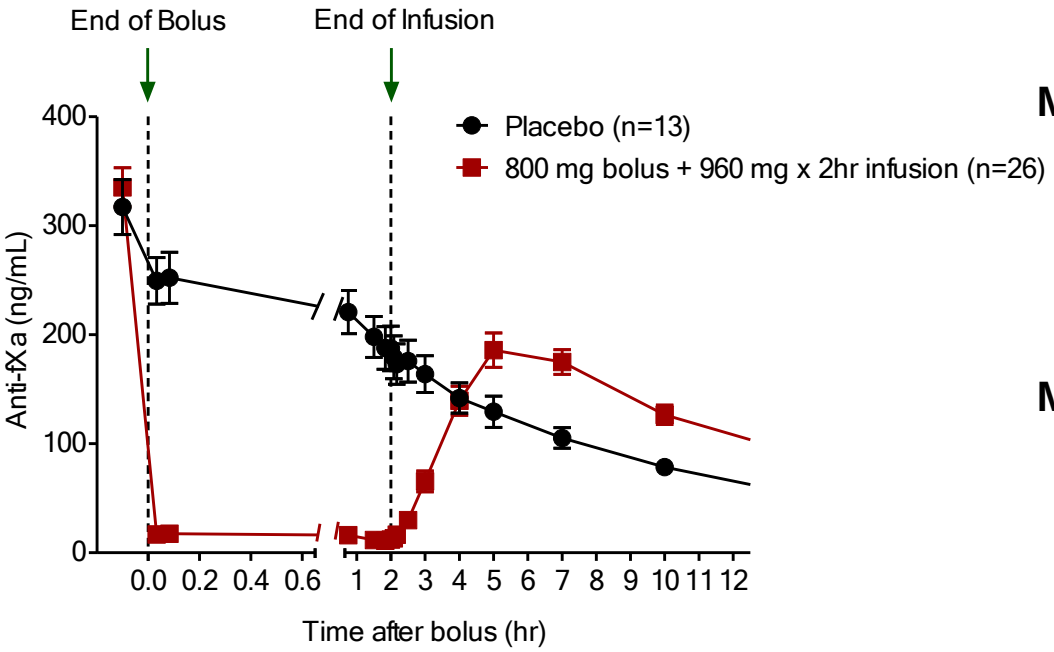
ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Safety: Andexanet Was Well-tolerated

- **All 39 subjects (26 andexanet, 13 placebo) completed study drug administration**
  - No subject experienced infusion-related reactions
- **No serious or severe adverse events were reported in any subject**
- **Transient increases in D-dimer (>2x ULN) and F1+2 were observed in a subset of subjects that generally returned to the normal range within 24-72 hours**
- **No thrombotic events**
- **No antibodies to factor X or factor Xa**
- **No neutralizing antibodies to andexanet**

Safety findings are consistent with previous Phase 2 and Phase 3 studies

ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Primary Endpoint: Anti-fXa

Anti-fXa (ng/mL)



Met Primary Endpoint:

- Mean percent change in anti-fXa from baseline to post-infusion nadir was 97%
- **p< 0.0001** *vs.* placebo

Met First Secondary Endpoint:

- Mean percent change in anti-fXa from baseline to post-bolus nadir was 95%
- **p< 0.0001** *vs.* placebo

Met Second Secondary Endpoint:

- Occurrence of subjects with ≥ 80% reduction in anti-fXa activity post-infusion nadir:
  AnXa (n= 26/26) *vs.* Placebo (n=0/13)
- **p< 0.0001** *vs.* placebo

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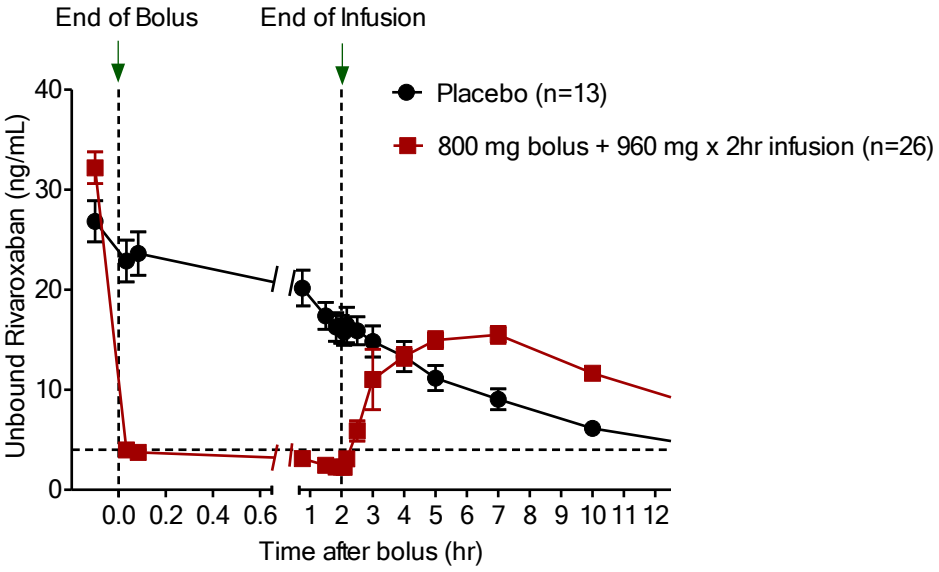
ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Secondary Endpoint: Unbound Rivaroxaban

Unbound Rivaroxaban (ng/mL)



Calculated unbound rivaroxaban no-effect level (4.0 ng/mL).

Met Third Secondary Endpoint:

- Mean change in free rivaroxaban concentration from baseline to post-infusion nadir (mean post-infusion nadir = 1.9 ng/mL)
- Mean free rivaroxaban concentration after andexanet administration was below calculated no-effect level (4.0 ng/mL)
- **p<0.0001** *vs.* placebo

Consistent with ANNEXA-R Part 1 (bolus only) and Phase 2 data

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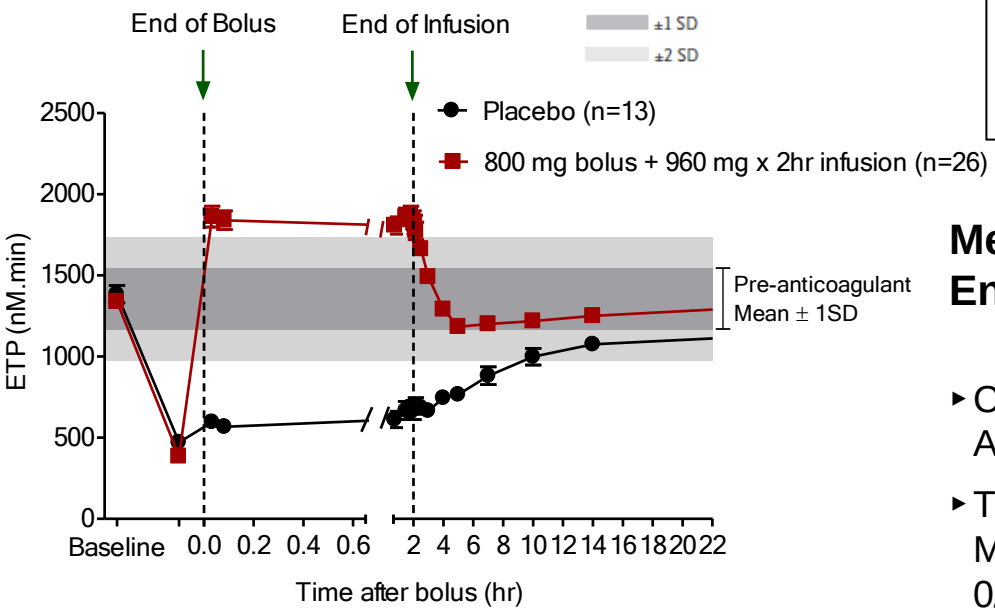
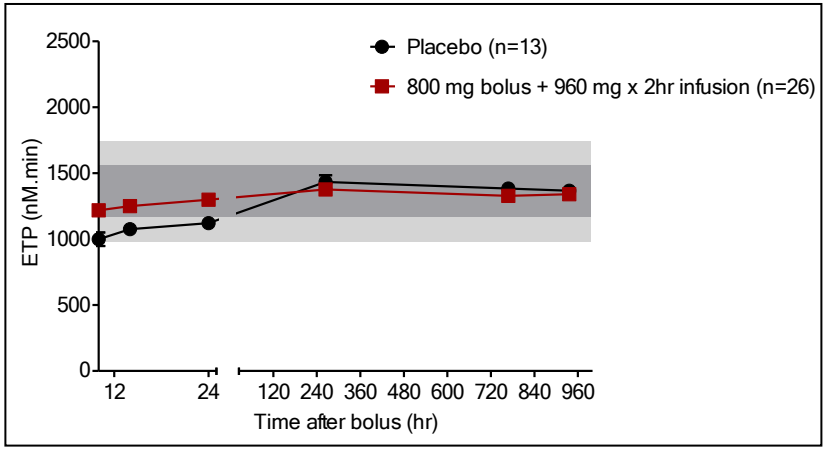
ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Secondary Endpoint: Thrombin Generation (ETP*)

Thrombin Generation





Met Fourth and Fifth Secondary Endpoints:

- Change in thrombin generation from pre-AnXa baseline to peak (**p< 0.0001**)
- Thrombin generation restored to above Mean - 1 SD in 26/26 of AnXa vs. 0/13 placebo subjects (**p< 0.0001**)

No Long Term Effect on Thrombin Generation (inset)

*ETP: Endogenous Thrombin Potential; Baseline: Day 1 Pre-rivaroxaban; Baseline range: Mean±1SD at Day 1 Pre-rivaroxaban

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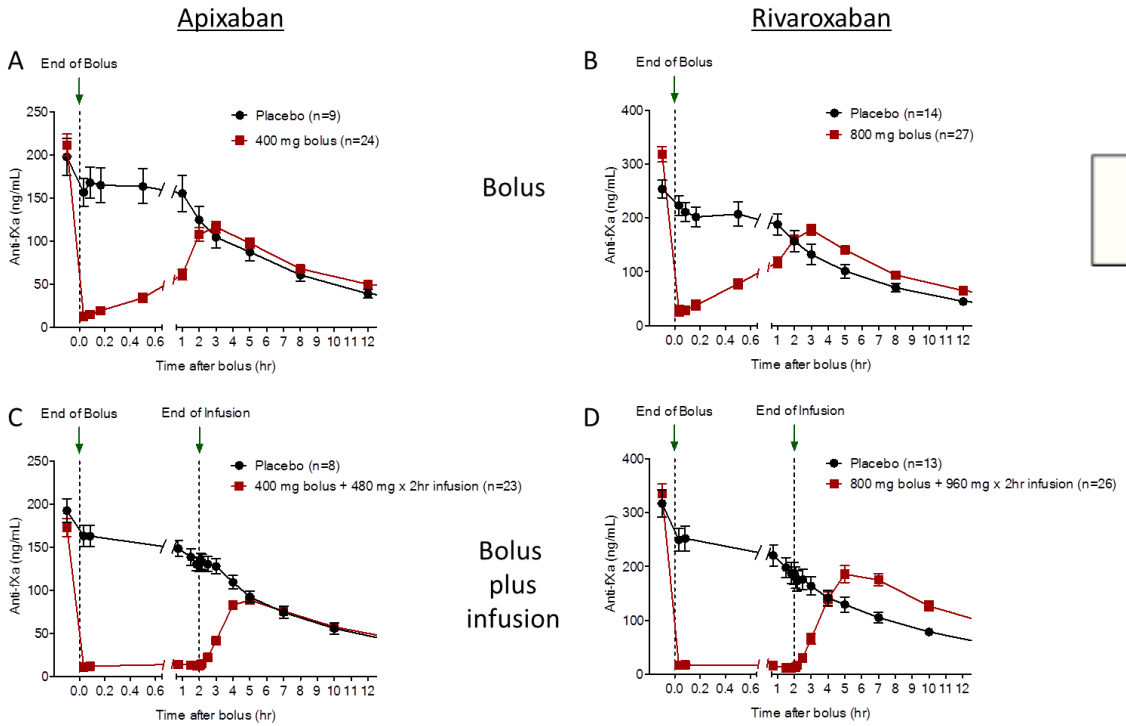
ANNEXA™-R (Rivaroxaban, Bolus + Infusion) Summary

- **Andexanet alfa administration:**
  - Was well-tolerated in older subjects aged 50-68
  - Met pre-specified primary efficacy endpoint ($p < 0.0001$)
  - Met all pre-specified secondary efficacy endpoints with high statistical significance
- **Andexanet rapidly reduced anti-fXa activity and free rivaroxaban, and restored thrombin generation to baseline (pre-rivaroxaban) levels.**
- **Andexanet produced near-complete normalization of coagulation parameters immediately post-bolus which was sustained during the 2hr-infusion.**
- **Reversal of coagulation biomarkers lasted 1-2 hours post-infusion in Part 2**

Publication of ANNEXA™-A and ANNEXA™-R Studies

- **The ANNEXA-A and ANNEXA-R study results are available online today at NEJM.org**



The NEW ENGLAND JOURNAL of MEDICINE

- Greater than 90% reversal of anti-fXa activity
- No serious or severe adverse events were reported in any subject
- No thrombotic events, antibodies to FX or FXa, or neutralizing antibodies to andexanet

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Andexanet Program Next Steps

- **FDA Biologics Licensing Application (BLA) planned by end of year**
- **Ongoing Phase 4 Outcomes Study in Bleeding Patients - ANNEXA™-4**
  - An ongoing open-label study in patients receiving fXa inhibitors presenting with acute major bleeding
  - Currently 33 sites with goal of >60 sites in North America and Europe
  - Planning for inclusion of patients on Apixaban, Rivaroxaban, Edoxaban and Enoxaparin
  - Two Primary Endpoints
    - First primary: Percent change from baseline in anti-fXa activity
    - Second primary: Occurrence of patients achieving “effective hemostasis” as adjudicated by an Independent Endpoint Adjudication Committee