ANNEXA™-A: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial, Demonstrating Reversal of Apixaban-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

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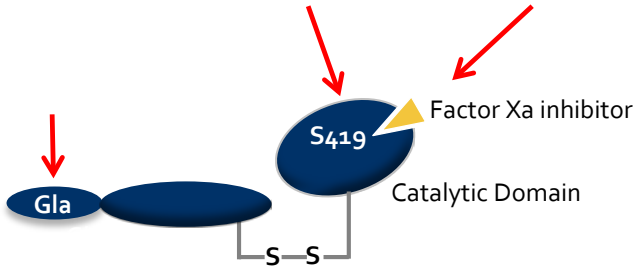
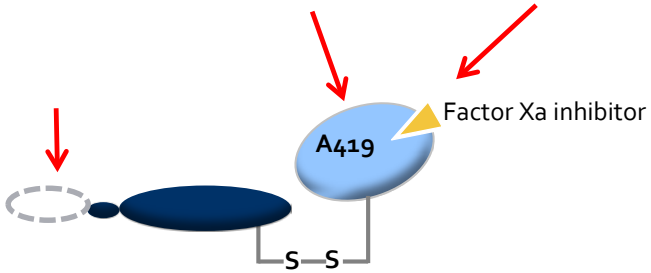
Andexanet: Designed to Reverse Activity of Factor Xa Inhibitors Through a Well-Defined Mechanism of Action

Recombinant engineered version of human factor Xa produced in CHO cells

- Acts as a fXa decoy and retains high affinity for all 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

- No known interaction with other coagulation factors except Tissue Factor Pathway Inhibitor (TFPI)
- No significant antibody signal found in development program to date

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Andexanet: Clinical Development Programs to Date Have Demonstrated Significant Reversal of PD Markers of fXa Inhibitors

- **Multiple Phase 2 Proof-of-Concept Studies**
  - ☑ Apixaban 5 mg PO Q12 - *completed*
  - ☑ Rivaroxaban 20 mg PO QD - *completed*
  - ☑ Enoxaparin 40 mg SQ QD – *completed*
    - 1 mg/kg SQ Q12 – *planned*
  - ☑ Edoxaban 60 mg PO QD – *ongoing*
  - ☐ Betrixaban 80 mg PO QD – *planned*

- **Phase 3 and Confirmatory Registration-enabling Studies**
  - ☑ Phase 3 studies: older healthy subjects – *ongoing*
  - ☐ Confirmatory study with bleeding patients

    - to be initiated end of 2014/early 2015

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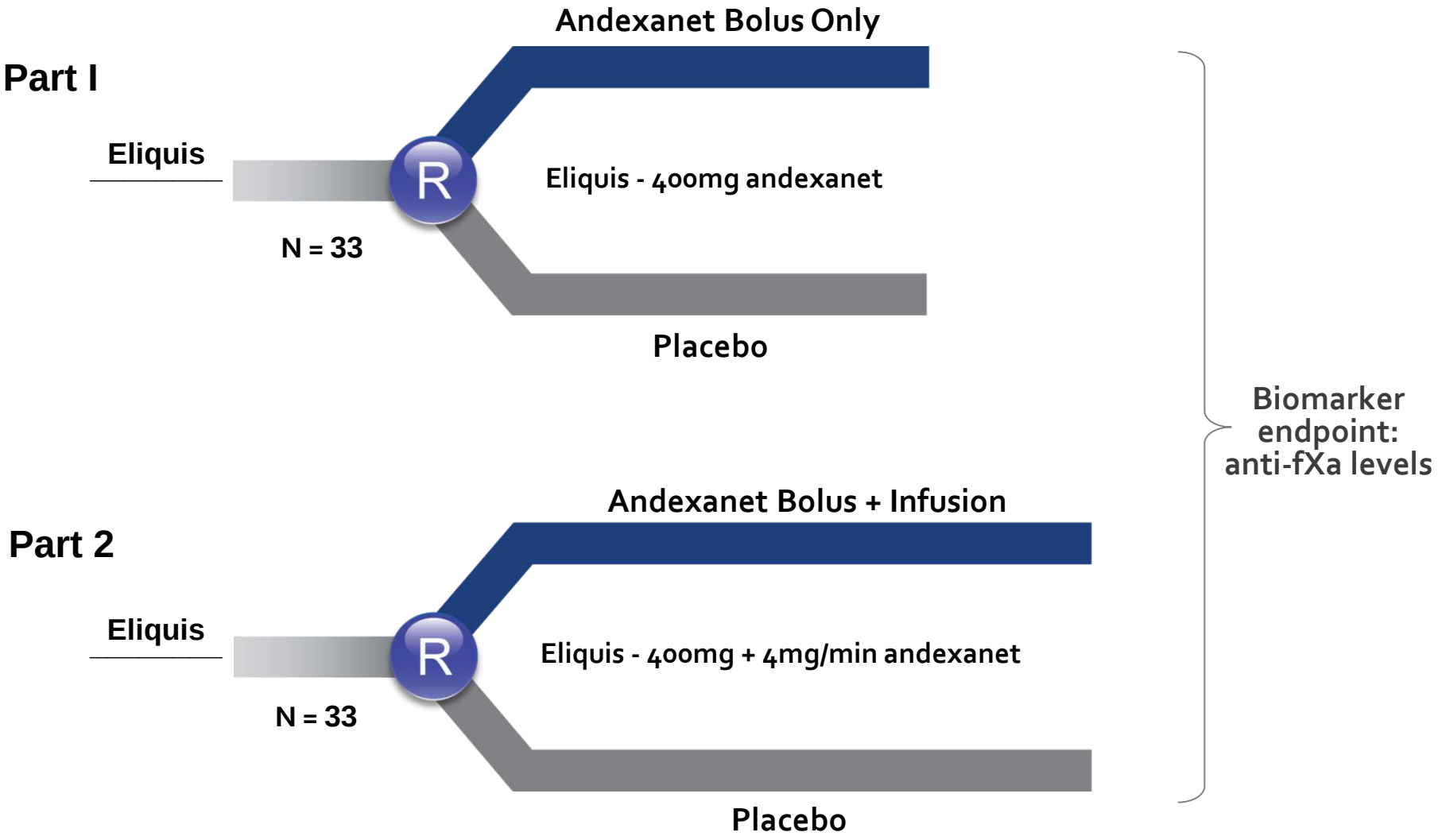
ANNEXA™
Phase 3 Registration-enabling Studies

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

ANNEXA – A: Apixaban
ANNEXA – R: Rivaroxaban

ANNEXA™-A: Apixaban (*Eliquis*)



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ANNEXA™-A (Apixaban, Part I)
Baseline Characteristics and Demographics

	Placebo (N = 9)	Andexanet (N = 24)
Sex, n (%) Male	6 (66.7%)	13 (54.2%)
Age, years		
Mean	59.0	61.0
SD	3.54	6.37
Median	58	60
Min, Max	55, 66	50, 73
Race, n (%) White	9 (100.0%)	24 (100.0%)
Ethnicity, n (%) Hispanic or Latino	4 (44.4%)	10 (41.7%)

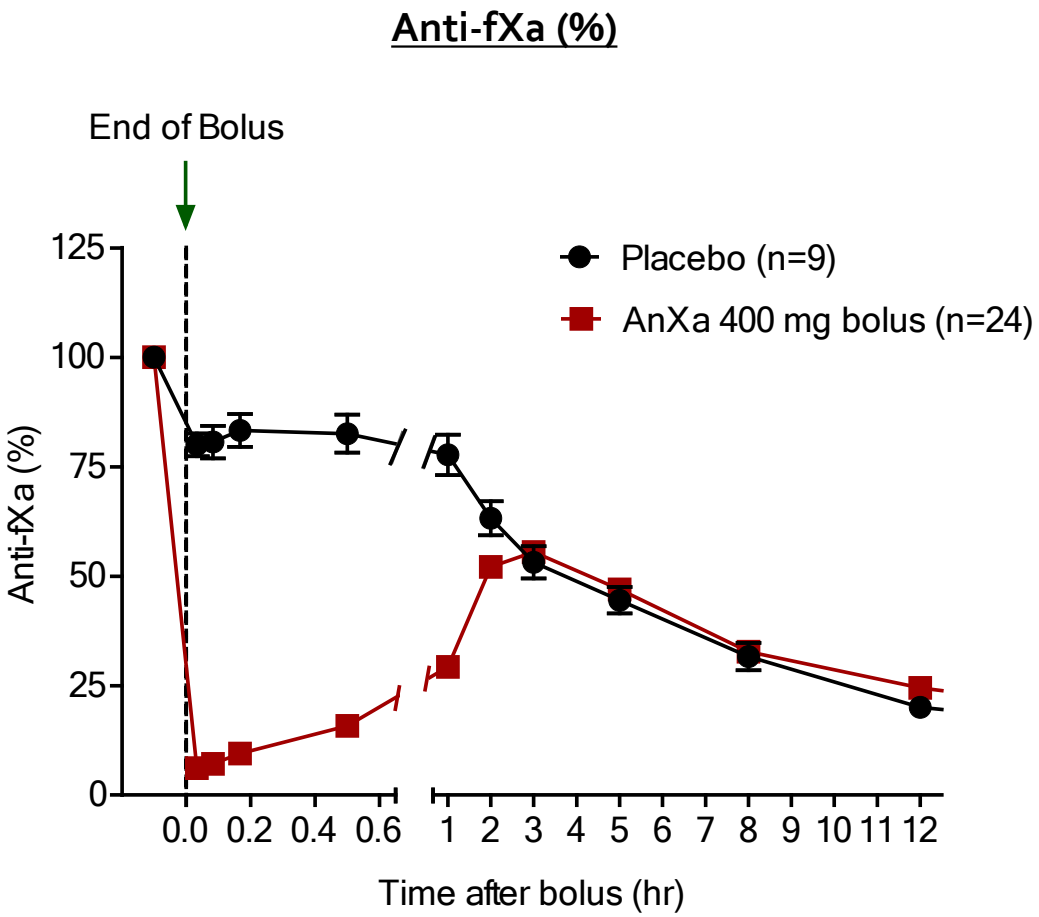
ANNEXA™-A (Apixaban, Part I)
Endpoints

- **Primary endpoint:**
  - Percent change in anti-fXa activity from baseline (measurement at peak concentration, before start of bolus) to nadir (smaller value of 2 or 5 minutes post end of bolus)
- **Secondary endpoints:**
  - Occurrence of 80% or greater reduction in anti-fXa activity from baseline to nadir
  - Change in free apixaban concentration from baseline to nadir
  - Change in thrombin generation from baseline to peak (largest value of 2, 5 or 10 minutes post end of bolus)

ANNEXA™-A (Apixaban, Part I)
Safety: Andexanet Was Well-tolerated

- **All 33 subjects completed the study**
  - 9 placebo, 24 andexanet
- **Safety data consistent with prior studies**
- **No serious or severe adverse events were reported in any subject**
- **No premature discontinuations from the study**
- **No thrombotic events**
- **No antibodies to factor X or factor Xa**

ANNEXA™-A (Apixaban, Part I) Primary Endpoint: Anti-fXa



- **Met Primary Endpoint:**
  - Percent change anti-fXa from baseline to nadir (= 94%)
    - p< 0.0001
- **Met first Secondary Endpoint:**
  - Number of subjects with > 80% reversal: andexanet (100%) *vs.* placebo (0%)
    - p< 0.0001
  - All andexanet subjects achieved ≥ 90% reversal

Data plotted as Mean ± SEM

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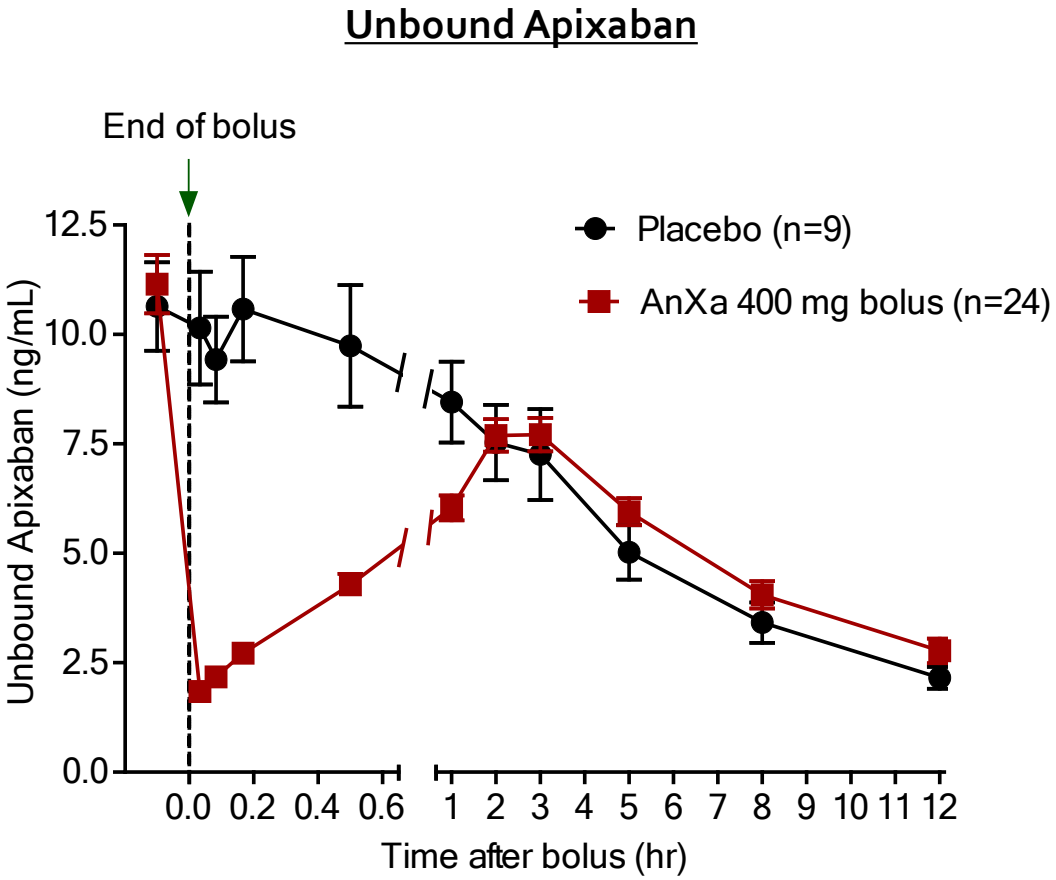
ANNEXA™-A (Apixaban, Part I)
Secondary Endpoint: Unbound Apixaban



- **Met second Secondary Endpoint:**
  - **Change in free apixaban concentration from baseline to nadir (= 1.8 ng/mL)**
    - **p< 0.0001**
- **Consistent with Phase 2 data**

Data plotted as Mean±SEM

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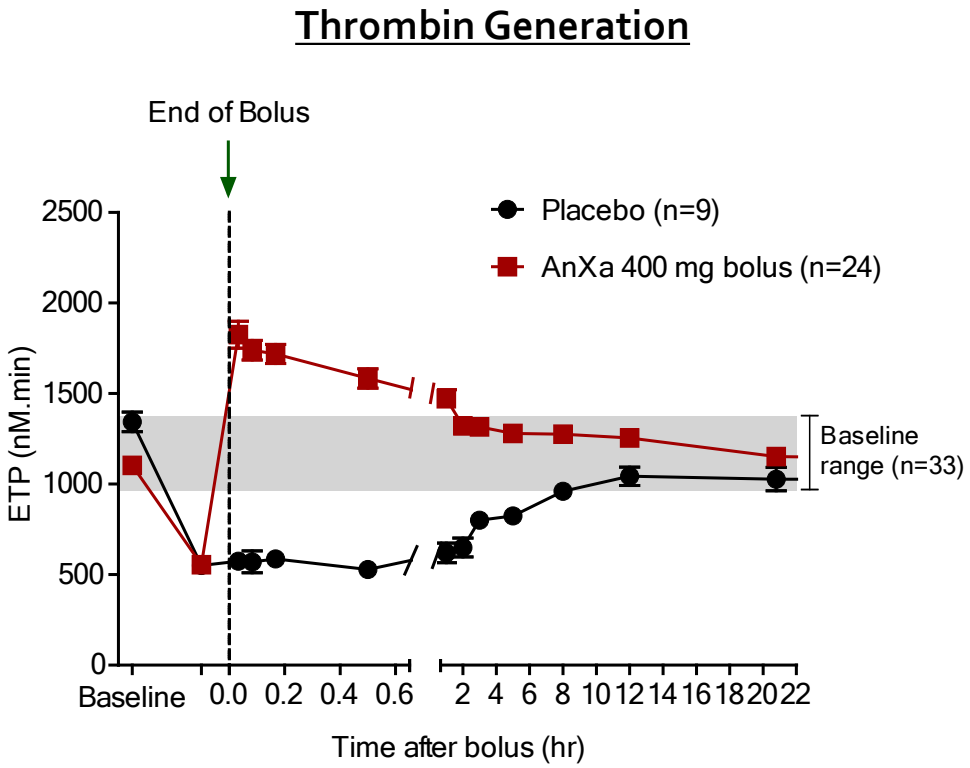
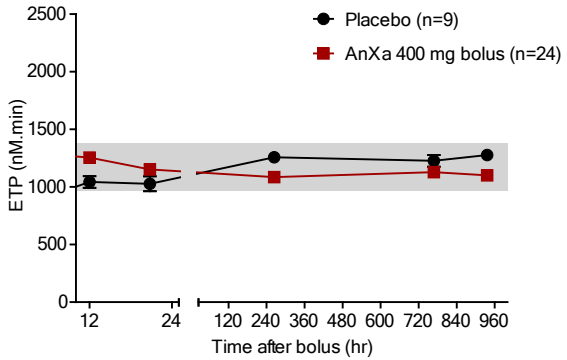
ANNEXA™-A (Apixaban, Part I)
Secondary Endpoint: Thrombin Generation (ETP*)





- **Met third Secondary Endpoint:**
  - **Change in thrombin generation from baseline to peak**
    - **p< 0.0001**
- **Thrombin generation return to baseline in 100% of AnXa subjects**
  - **No rebound effect on thrombin generation after andexanet and/or apixaban were cleared**

*ETP: Endogenous Thrombin Potential
Data were plotted as Mean±SEM; Baseline ranges was based on Mean± 1 SD at Day1 Predose (n=33)

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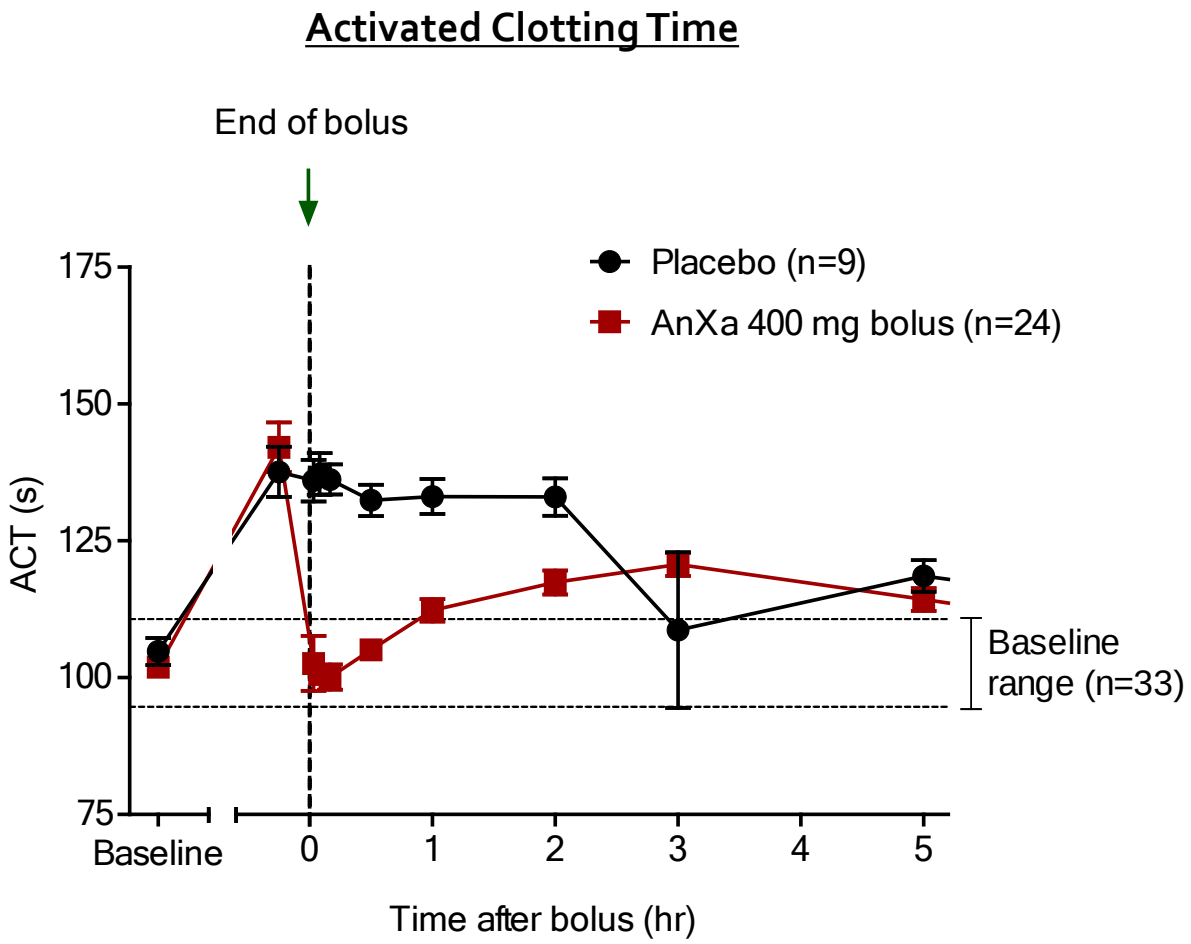
ANNEXA™-A (Apixaban, Part I) Activated Clotting Time (ACT)



- **Apixaban-induced prolongation of ACT was corrected to baseline range**

Data plotted as Mean±SEM; Baseline range was based on Mean±1 SD at screen (n=33).

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ANNEXA™-A (Apixaban, Part I)
Summary

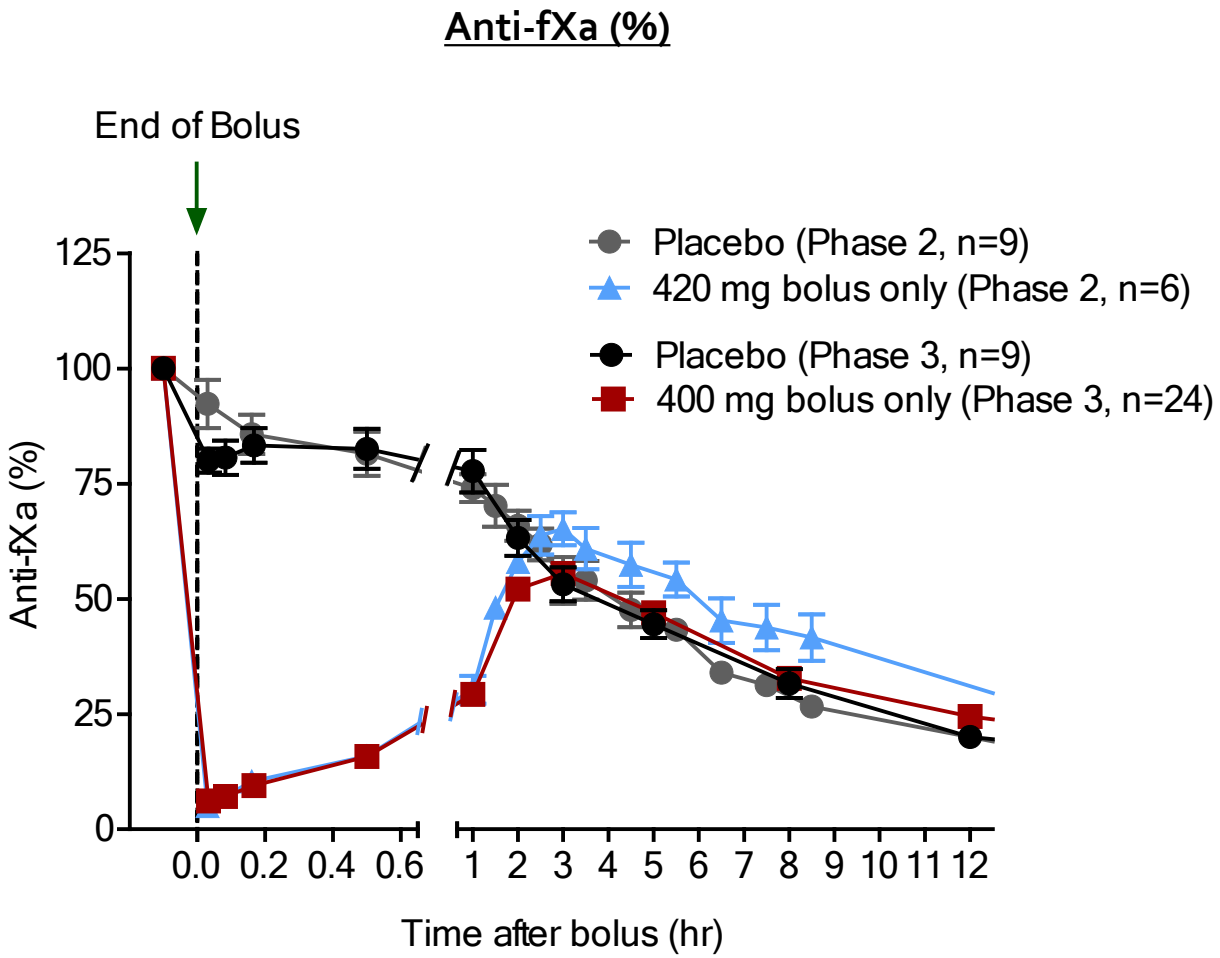
- **Andexanet alfa administration:**
  - Was well-tolerated in older subjects aged 55-73
  - Met all pre-specified primary and secondary efficacy endpoints with $p < 0.0001$
- **100% of andexanet treated subjects had ≥ 90% reversal of anti-fXa activity and restoration of thrombin generation to baseline (pre-anticoagulant) levels**
- **Andexanet produced near complete normalization of all coagulation parameters measured within 2 minutes of completion of infusion**
  - Effect lasted 1-2 hours with bolus dose in Part I
  - The focus of Part 2 of the ANNEXA-A Phase 3 study will be to demonstrate that prolonged reversal can be sustained with continuous infusion after bolus

ANNEXA™
Next Studies

- **ANNEXA™-A (Apixaban): Part I (bolus only)**
  - Current presentation
- **ANNEXA™-A (Apixaban): Part 2 (bolus *plus* infusion)**
  - LPLV: *completed*
  - Topline Data: first half 2015
- **ANNEXA™-R (Rivaroxaban): Part I (bolus only)**
  - LPLV: *completed*
  - Topline Data: Q4, 2014
- **ANNEXA™-R (Rivaroxaban): Part 2 (bolus *plus* infusion)**
  - FPFV: Planned to be initiated end of November 2014
  - Topline Data: first half 2015

Backup

Comparison to Phase 2 POC Data
Anti-fXa



Data were plotted as Mean±SEM; %Baseline was expressed as group mean of individually normalized numbers.

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