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

Mark Crowther, MD, MSc, FRCPC

Professor of Medicine, McMaster University, Canada

Co-authors

Gallia Levy¹, Genmin Lu¹, Janet Leeds¹, Brian Wiens¹, Lee Barron¹, Pamela B. Conley¹, Janice Castillo¹, Alex Gold¹, John T. Curnutte¹, Stuart Connolly²

¹Portola Pharmaceuticals employee; ²Portola Pharmaceuticals consultant
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 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

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

Andexanet

- No significant antibody signal found in development program to date
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
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)

Part I

- **Eliquis**
  - Andexanet Bolus Only
    - Eliquis - 400mg andexanet
    - Placebo
    - N = 33

Part 2

- **Eliquis**
  - Andexanet Bolus + Infusion
    - Eliquis - 400mg + 4mg/min andexanet
    - Placebo
    - N = 33

Biomarker endpoint: anti-fXa levels
## ANNEXA™-A (Apixaban, Part I)
### Baseline Characteristics and Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 9)</th>
<th>Andexanet (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, n (%) Male</strong></td>
<td>6 (66.7%)</td>
<td>13 (54.2%)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>59.0</td>
<td>61.0</td>
</tr>
<tr>
<td>SD</td>
<td>3.54</td>
<td>6.37</td>
</tr>
<tr>
<td>Median</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>Min, Max</td>
<td>55, 66</td>
<td>50, 73</td>
</tr>
<tr>
<td><strong>Race, n (%) White</strong></td>
<td>9 (100.0%)</td>
<td>24 (100.0%)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%) Hispanic or Latino</strong></td>
<td>4 (44.4%)</td>
<td>10 (41.7%)</td>
</tr>
</tbody>
</table>
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 \( \geq 90\% \) reversal
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
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)
ANNEXA™-A (Apixaban, Part I)
Activated Clotting Time (ACT)

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

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