Andexanet Alfa, an Investigational Universal Antidote for Reversal of Anticoagulation of Factor Xa Inhibitors in Healthy Human Volunteers

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Introduction

- Although direct factor Xa (FXa) inhibitors have demonstrated superior or comparable anticoagulant efficacy and/or safety compared with warfarin, risk of bleeding is a major clinical concern.
- No specific antidotes are available to reverse the anticoagulant effects of FXa inhibitors during episodes of major bleeding or prior to emergency surgery.
- Andexanet alfa, a recombinant modified FXa, is an antidote designed for reversal of FXa inhibitors.
- Andexanet is currently being evaluated in a Phase 3b/4 Confirmatory (ANNEXA-4) study in patients who experince acute major bleeding.
- We report data from the ANNEXA™ Phase 3 registration studies in older healthy subjects anticoagulated with apixaban or rivaroxaban.

Methods

- ANNEXA–A&R were two Phase 3, randomized, double-blind, placebo-controlled studies of andexanet in healthy subjects age 50-75 administered either apixaban or rivaroxaban (**Figure 1**).
- Andexanet dose selection is based on Phase 2 data and PK/PD modeling (**Table 1**).
- In ANNEXA™-A, subjects were treated with apixaban 5 mg BID for 4 days to achieve steady state concentrations. Andexanet (400 mg bolus or 400 mg bolus plus 4 mg/min x 2-h infusion) or placebo was administered on Day 4, 3 h after the last apixaban dose.
- In ANNEXA™-R, subjects were treated with rivaroxaban 20 mg QD for 4 days to achieve steady state concentrations. Andexanet (800 mg bolus or 800 mg bolus plus 8 mg/min x 2-h infusion) or placebo was administered on Day 4, 4 h after the last rivaroxaban dose.
- The primary efficacy endpoint was percent change from baseline in anti-FXa activity to nadir (between 2-5 min post-bolus or between 10 min prior to and 5 min after the end of the continuous infusion).
- Additional efficacy endpoints included reduction in plasma unbound inhibitor concentration and restoration of thrombin generation.
- Safety data were collected through Day 43.

Figure 1. Trial Design

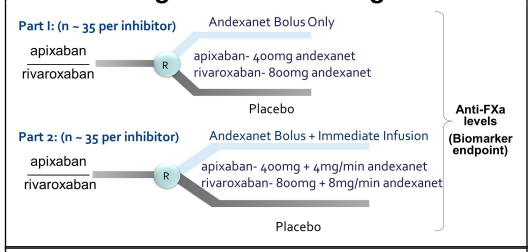


Table 1. Andexanet Dose Nomogram for FXa Inhibitors

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose before Andexanet Initiation	
		< 8 h or Unknown	≥ 8 h
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	>10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	>5 mg / Unknown	High Dose	
Enoxaparin	≤ 40 mg	Low Dose	
	> 40 mg / Unknown	High Dose	
Edoxaban	≤ 60 mg	High Dose	
Unknown	Unknown	High Dose	

Dose	Initial IV Bolus	Immediate Follow on IV Infusion
Low Dose	400 mg at 30 mg/min	4 mg/min for up to 120 min
High Dose	800 mg at 30 mg/min	8 mg/min for up to 120 min

Results

- ANNEXA-A&R enrolled 63 and 82 subjects, respectively. Baseline chracteristics are presented in **Table 2**.
- For the primary efficacy endpoint, there was a significant difference ($p<0.001$) in the percent change in anti-FXa activity (relative to the pre-bolus activity level) between andexanet and placebo until 2 h after administration of the bolus or end of the infusion (**Figure 2**).
- For additional efficacy endpoints, there was a significant difference ($p<0.05$) in the reduction in unbound plasma anticoagulant levels between andexanet and placebo until 2 h after the end of the bolus and 1 h after the end of the infusion in the apixaban study, and until 3 h after the end of the bolus or infusion in the rivaroxaban study (**Figure 3**). Unbound plasma concentrations of FXa inhibitors were below or at the level of the calculated no-effect for apixaban (3.5 ng/mL,) or rivaroxaban (4.0 ng/mL) (dashed horizontal lines in Figure 3).
- There was also a significant difference ($p<0.001$) in restoration of thrombin generation between andexanet and placebo for at least 12 h after administration of the bolus or end of the infusion (**Figure 4**).

Table 2. Baseline Characteristics and Demographics

ANNEXA™-A&R	Apixaban (Andexanet:Placebo=3:1)				Rivaroxaban (Andexanet:Placebo=2:1)			
	Part 1 (bolus only)		Part 2 (bolus + infusion)		Part 1 (bolus only)		Part 2 (bolus + infusion)	
	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo	Andexanet	Placebo
N	24	9	24	8	27	14	26	13
Age, Median (Yr)	60.0	58.0	56.0	58.5	56.0	53.5	56.0	57.0
Female sex, N (%)	11 (45.8)	3 (33.3)	7 (29.2)	3 (37.5)	9 (33.3)	6 (42.9)	11 (42.3)	6 (46.2)
BMI, Mean (SD)	26.7 (2.5)	27.4 (2.5)	27.5 (2.1)	27.8 (2.4)	27.0 (3.4)	25.9 (3.4)	27.8 (3.0)	27.6 (2.6)
Creatinine, Mean (SD) (mg/dL)	0.8 (0.2)	0.8 (0.1)	0.9 (0.2)	0.9 (0.2)	0.9 (0.2)	0.8 (0.2)	0.9 (0.2)	0.9 (0.2)
Race, N (%) White	24 (100)	9 (100)	21 (87.5)	8 (100)	22 (81.5)	10 (71.4)	20 (76.9)	8 (61.5)
Ethnicity, N (%) Hispanic or Latino	10 (41.7)	4 (44.4)	11 (45.8)	2 (25)	9 (33.3)	4 (28.6)	4 (30.8)	10 (38.5)

Figure 2. Reversal of Ant-FXa Activity

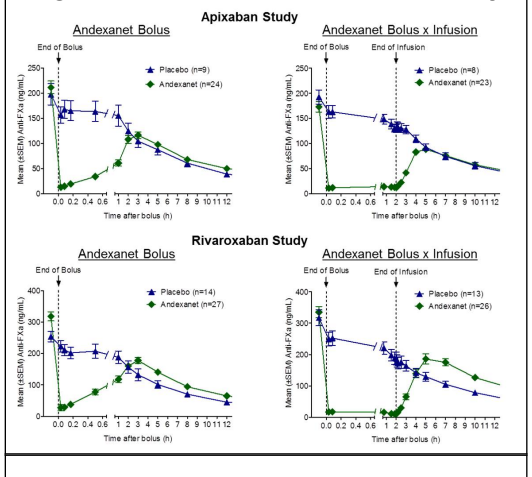


Figure 3. Reduction of Unbound Inhibitor

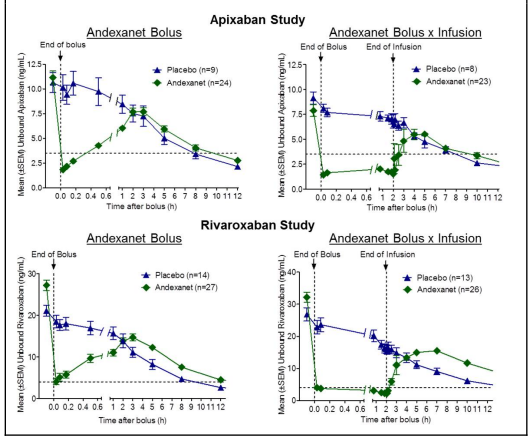
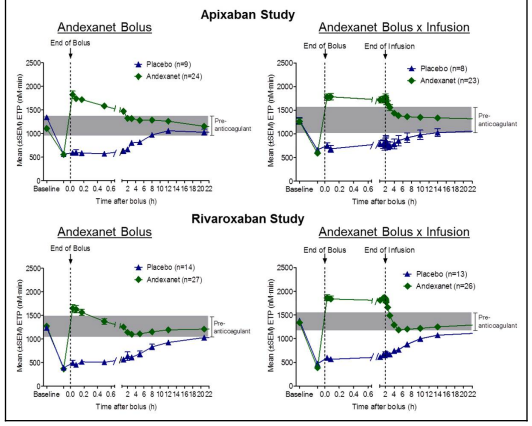


Figure 4. Restoration of Thrombin Generation



Safety

- There were no serious/severe adverse events or thrombotic events. One andexanet subject discontinued infusion due to mild hives.
- There were no antibodies to endogenous FX or FXa, and no neutralizing antibodies to andexanet. Low titer, non-neutralizing antibodies were detected in subset of subjects.
- There were transient elevations of F1+2 and D-dimer without clinical manifestations.

Conclusions

- ANNEXA-A&R studies in healthy subjects achieved all primary and secondary endpoints.
- Administration of andexanet resulted in a rapid and sustained reduction in anti-FXa activity and unbound anticoagulant levels, and in restoration of hrombin generation to baseline (pre-anticoagulant) levels.
- Andexanet was well-tolerated in healthy subjects.
- A Phase 3b/4 confirmatory study (ANNEXA-4) in patients with acute major bleeds is ongoing.
- Andexanet has the potential to be a universal reversal agent for both direct and indirect FXa inhibitors.

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References

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