Andexanet Alfa for Reversal of Anticoagulation in Factor Xa–associated Acute Major Bleeding: Interim Report From the ANNEXA-4 Study

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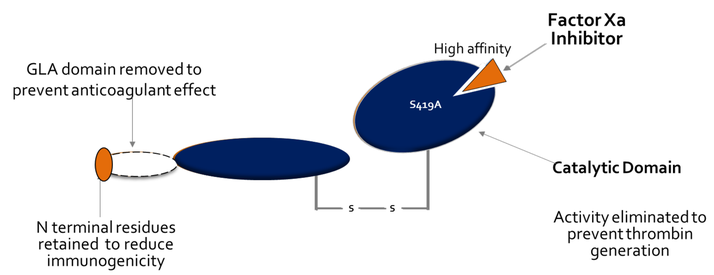
Background

- Factor Xa (FXa) inhibitors reduce thrombotic events, but can precipitate major bleeding
  - Over 50,000 patients experience major bleeding across Europe (*PREFER in VTE* registry, 2013-2015)
  - Fatality rate due to major bleeding is 15% to 20%
- Andexanet alfa (Andexxa) was developed as a specific reversal agent for direct and indirect FXa inhibitors (**Figure 1**), and has been approved in the United States for reversal of rivaroxaban and apixaban anticoagulation due to life-threatening or uncontrolled bleeding
- Andexanet rapidly reversed anticoagulation effects, assessed by anti-FXa activity, in healthy volunteers

Figure 1. Andexanet alfa: FXa decoy



Objective

- To assess the efficacy and safety of andexanet alfa in bleeding patients anticoagulated with FXa inhibitors in the ongoing ANNEXA-4 clinical trial

Patients & Methods

- Study Design
  - ANNEXA-4 is an ongoing prospective, open-label, single-arm study of andexanet in patients with acute major bleeding while taking an FXa inhibitor
  - Eligible patients are >18 years, and have acute major bleeding within 18 hours of their last FXa inhibitor dose (**Figure 2**)
  - Enrolled patients are treated with either 400 or 800 mg andexanet bolus followed by a 4 or 8 mg/min infusion for 2 hours, based on FXa inhibitor received, dose, and time since last dose (**Figure 3**)
- Analysis Populations
  - Safety population includes all patients with acute major bleeding receiving andexanet
  - Efficacy population excludes patients with baseline anti-FXa activity <75 ng/mL (<0.25 IU/mL for enoxaparin)
- Interim Report
  - Includes all patients as of October 20, 2017
  - All cases assessed by independent adjudication committee
- Assessment of Clinical Hemostatic Efficacy
  - Independent Core Lab interpreted brain CT and MRI
  - Cases rated as excellent/good versus poor/none based on specific criteria
  - This methodology was initially developed for assessment of 4F-PCC in warfarin bleeding, where efficacy reported was 72%*

*Sarode et al. *Circulation.* 2013;128:1234-43.

Figure 2. ANNEXA-4 study design

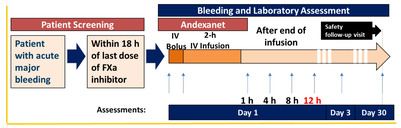
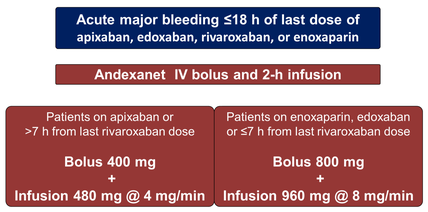


Figure 3. ANNEXA-4 dose selection



Results

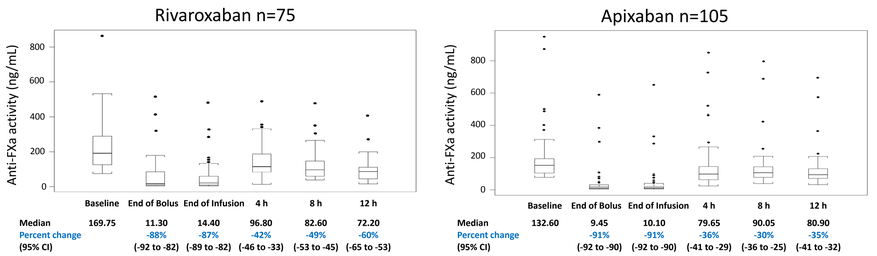
Table 1. Baseline characteristics

	Safety Population n=227	Efficacy Population n=137
Age (y), mean ± SD	77 ± 11	77 ± 12
Male	117 (52%)	70 (51%)
Time from presentation until andexanet (h)	4.7 ± 2.8	5.0 ± 3.1
Estimated creatinine clearance <30 mL/min	21 (9%)	13 (10%)
Indication for anticoagulation		
Atrial fibrillation	178 (78%)	104 (76%)
Venous Thromboembolic Disease	52 (23%)	38 (28%)
Atrial fibrillation and VTE	8 (4%)	6 (4%)
Medical history		
Myocardial infarction	32 (14%)	15 (11%)
Stroke	47 (21%)	32 (23%)
Heart failure	52 (23%)	36 (26%)
Diabetes mellitus	67 (30%)	42 (31%)

Table 2. Site of initial bleeding

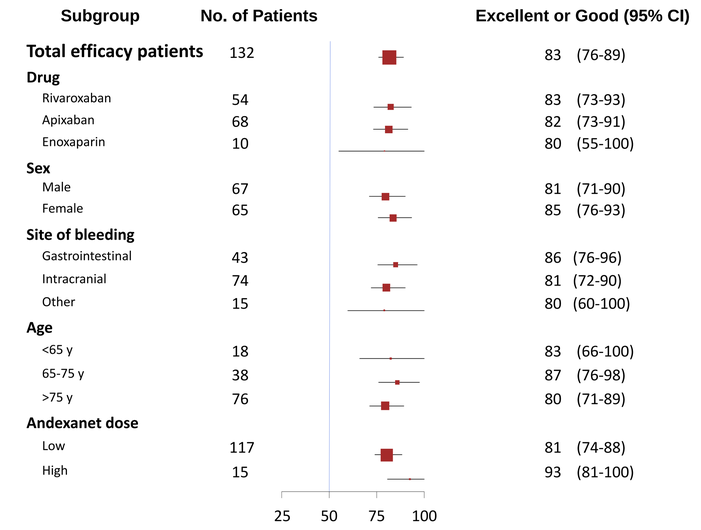
	Safety Population n=227	Efficacy Population n=137
Intracranial bleeding	139 (61%)	78 (57%)
Glasgow Coma Scale, mean ± SD	13.9 ± 1.63	13.9 ± 1.70
Intracerebral site	74 (52%)	44 (54%)
Sub-dural site	45 (32%)	24 (30%)
Subarachnoid site	23 (16%)	13 (16%)
Gastrointestinal bleeding	62 (27%)	43 (31%)
Other bleeding site	26 (12%)	16 (12%)

Figure 4. Anti-FXa activity



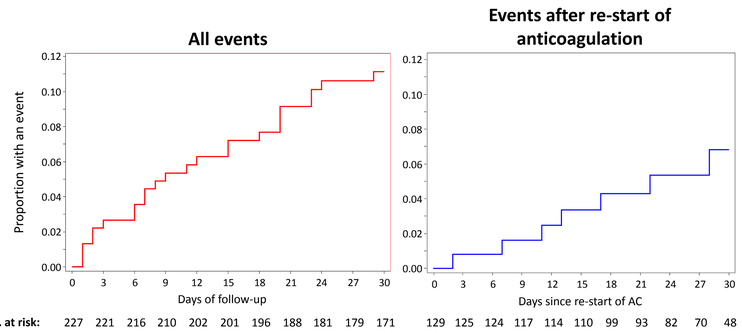
- Among efficacy evaluable patients, the reduction in median anti-FXa activity with andexanet was 92% (**Figure 4**)
- At 12 hours post-andexanet, there were 132 major bleeds adjudicated; 109 (83%) patients achieved excellent or good hemostasis (**Figure 5**)

Figure 5. Clinical hemostatic efficacy



- Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and in 24 (11%) patients by 30 days
- Anticoagulation was re-started in 129 (57%) patients by 30 days (**Figure 6**)
  - Therapeutic anticoagulation was re-started in 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

Figure 6. Thrombotic events



Conclusions

- Andexanet alfa rapidly reversed anti-FXa activity in bleeding patients
- Effective hemostasis was achieved in 83% of patients
- Thrombotic events/mortality rates were consistent with the high risk profile of the patient population
- The full analysis of the ANNEXA-4 trial in 2019 will provide efficacy and safety data for reversal of anticoagulation with andexanet alfa in patients with acute major bleeding while anticoagulated with a FXa inhibitor