Validation of the Regimen With Andexanet Alfa for Reversal of Anticoagulation in Patients With Acute Major Bleeding

Janet M. Leeds,[1] Yuan Xiong,[2] Mark Lovern,[2] Kenneth Der,[1] Jaap W. Mandema,[2] Genmin Lu,[1] John T. Curnutte,[1] Truman J. Milling,[3] Mark Crowther,[4] Stuart J. Connolly,[4] Patrick Yue,[1] Pamela B. Conley,[1] Iwona Bucior[1]

[1]Portola Pharmaceuticals, Inc., South San Francisco, CA, USA; [2]Certara, Inc., Princeton, NJ, USA; [3]Seton Dell Medical School Stroke Institute, Austin, TX, USA; [4]McMaster University, Hamilton, Canada

Background

- Andexanet alfa (Andexxa) is a recombinant protein that acts as a factor Xa (FXa) decoy to bind and sequester FXa inhibitors (e.g., apixaban, rivaroxaban, edoxaban, betrixaban, or enoxaparin); it binds FXa inhibitors and counteracts their activity but is no longer capable of assembly into the prothrombinase complex (**Figures 1 and 2**)
- It is approved in the US for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
- The regimen with andexanet alfa (**Table 1**) was informed by a pharmacokinetic (PK)/pharmacodynamic (PD) model developed in phase 2 studies in healthy subjects
- The PK of direct FXa inhibitors (defined by equilibrium between plasma, interstitial and lymphatic fluids, and tissues) and the effect of andexanet on PK of FXa inhibitors are key parameters in the PK/PD model (**Figure 3**)
- The PK/PD model has been recently refined by assessing the effect of intrinsic factors (renal function, age, and body weight) on both FXa and andexanet exposure

Objective

- The goal of this analysis was to validate the dosing of andexanet alfa by comparing the projected efficacy data assessed by the refined PK/PD model with observed data obtained from bleeding patients in an ongoing ANNEXA-4 trial

Methods

- ANNEXA-4 is an ongoing, prospective, open-label study in which bleeding patients anticoagulated with a FXa inhibitor received IV andexanet bolus (400 or 800 mg) followed by 120-minute infusion (4 or 8 mg/min; **Figure 4**)
- Anti-FXa activity was measured before andexanet administration (baseline), at end of bolus (EOB), at end of infusion (EOI), and at 4, 8, and 12 hours after infusion
- The percent reversal of anti-FXa activity was projected by the refined PK/PD model in healthy subjects and then compared with the percent reversal of anti-FXa activity in patients with acute major bleeding

Figure 1. Andexanet alfa: recombinant modified human FXa designed to reverse anticoagulation activity of FXa inhibitors

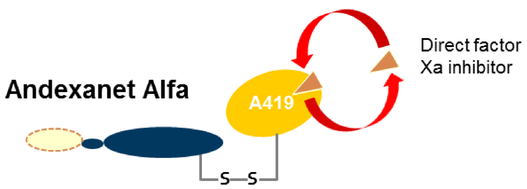


Table 1. Andexanet alfa dosing regimen

Dose*	Initial IV bolus	Follow-on IV infusion	
Low dose	400 mg at a target rate of 30 mg/min	4 mg/mL for up to 120 minutes	
High dose	800 mg at a target rate of 30 mg/min	8 mg/mL for up to 120 minutes	
FXa inhibitor	FXa inhibitor last dose	Timing of FXa inhibitor last dose before andexanet alfa initiation	
		<8 hours or unknown	≥8 hours
Rivaroxaban	≤10 mg	Low dose	Low dose
	>10 mg/unknown	High dose	
Apixaban	≤5 mg	Low dose	
	>5 mg/unknown	High dose	

*The safety and effectiveness of >1 dose have not been evaluated.

Figure 2. Site of action for FXa inhibitors

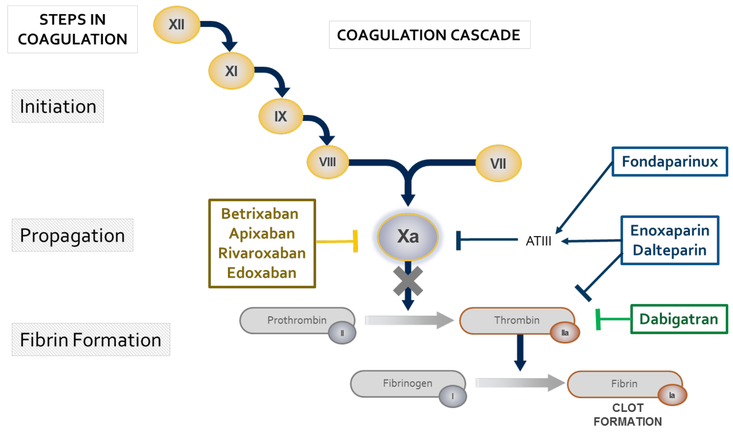
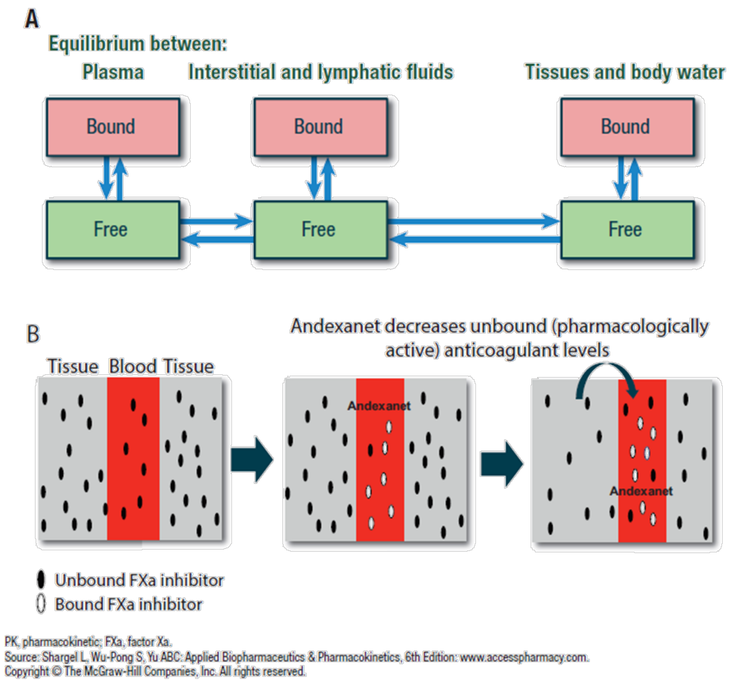
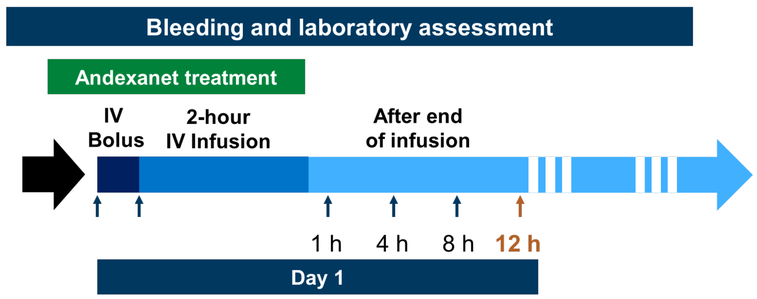


Figure 3. PK of direct FXa inhibitors (A) and effect of andexanet alfa on the PK of FXa inhibitors (B)



PK, pharmacokinetic; FXa, factor Xa.
Source: Shargel L, Wu-Pong S, Yu ABC: Applied Biopharmaceutics & Pharmacokinetics, 6th Edition: www.accesspharmacy.com.

Figure 4. ANNEXA-4 study design



Results

- Plasma samples from 139 patients (apixaban, 76; rivaroxaban, 63) were available for comparisons with the refined PK/PD model
- For rivaroxaban, mean percent reversal of anti-FXa activity in bleeding patients was similar to that predicted by the PK/PD model (**Table 2**)
- For apixaban, mean percent reversal of anti-FXa activity in bleeding patients was similar at EOB and EOI to that predicted by the PK/PD model (**Table 3**)
- After 4 hours, the observed reversal of anti-FXa activity for apixaban diverged between projected and observed values.

Table 2. Percent reversal of anti-FXa activity for rivaroxaban

Protocol time	n	Observed % reversal		Predicted % reversal	
		Median	90% CI	Median	90% CI
End of bolus	48	**88.9**	27.0, 97.9	**87.6**	48.4, 96.5
End of infusion	50	**86.9**	38.2, 97.8	**85.8**	41.4, 97.5
4-hour assessment	60	**43.9**	14.2, 71.2	**26.8**	8.9, 61.6
8-hour assessment	61	**50.4**	15.3, 69.1	**45.8**	24.2, 67.7
12-hour assessment	63	**63.4**	18.0, 81.5	**61.5**	39.9, 80.4

Table 3. Percent reversal of anti-FXa activity for apixaban

Protocol time	n	Observed % reversal		Predicted % reversal	
		Median	90% CI	Median	90% CI
End of bolus	61	**91.7**	67.4, 95.7	**94.8**	88.6, 97.0
End of infusion	64	**91.5**	65.9, 95.0	**94.0**	87.5, 96.5
4-hour assessment	74	**38.6**	3.8, 73.6	**48.7**	29.1, 72.8
8-hour assessment	75	**33.0**	11.7, 56.1	**49.1**	31.0, 68.9
12-hour assessment	76	**37.3**	18.1, 61.9	**55.7**	36.1, 75.2

Conclusions

- The final, refined PK/PD model in healthy subjects predicted the level of anticoagulation reversal in bleeding patients, assessed by reductions in anti-FXa activity, and validated the andexanet alfa regimen required to reverse anticoagulation by FXa inhibitors
- The predictions were within the 90% confidence intervals for rivaroxaban and apixaban at all time points
- The apixaban PK/PD model overpredicted anticoagulation reversal at later times, possibly due to high baseline anti-FXa activity levels in some apixaban patients