Validation of the PK/PD Model Used for Dose Selection of Andexanet Alfa for Reversal of Anticoagulation

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Background

- Andexanet alfa (andexanet) is a catalytically inactive derivative of factor Xa (FXa) that binds and sequesters direct FXa inhibitors (e.g., apixaban, rivaroxaban, edoxaban, or betrixaban) thereby reversing their anticoagulant activity.
- Andexanet is approved in the United States for patients anticoagulated with rivaroxaban and apixaban, when reversal is needed due to life-threatening or uncontrolled bleeding.
- The dosing regimen was informed by a pharmacokinetic (PK)/ pharmacodynamic (PD) model developed in studies in healthy subjects.
- A critical aspect of the structure of the PK/PD models is the central compartment binding interaction of andexanet and the FXa inhibitors (**Figure 1**).
- An update of the PK/PD models takes into account the effect of intrinsic factors (renal function, age, and body weight) on both FXa and andexanet exposure, using covariates for FXa inhibitors identified in patients.

Figure 1. Structure of PK/PD Models of Andexanet With FXa Inhibitor (Apixaban or Rivaroxaban)

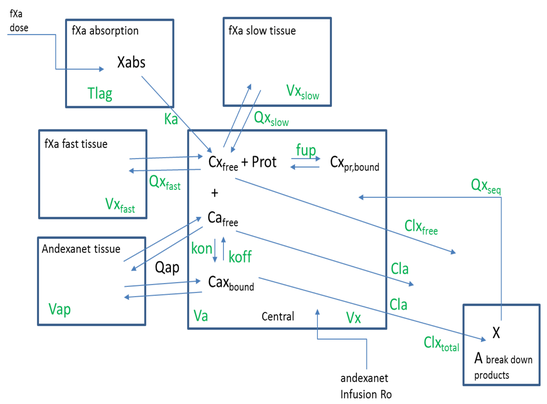


Table 1. Assumptions, Definitions, and Parameters for Andexanet-FXa Inhibitor Models

Model Assumptions

- PK of andexanet not affected by the FXa inhibitor
- 1:1 binding of andexanet and the FXa inhibitor
- Fast binding
- Only the free (unbound) FXa inhibitor is eliminated

Definitions

- Cx_{free} = Free concentration of inhibitor (umol/L)
- Cx_{total} = Total concentration of inhibitor (umol/L)
- Cax_{bound} = Bound concentration of inhibitor and andexanet (umol/L)
- Ca_{free} = Free concentration of andexanet (umol/L)
- $Cx_{pr,bound}$ = Protein bound concentration of inhibitor (umol/L)

Parameters

- CLa: clearance of andexanet
- Va: central volume of andexanet
- Qap: distributional clearance of andexanet
- Vap: tissue volume of andexanet
- CLx_{free}: intrinsic clearance of free inhibitor
- CLx_{total}: intrinsic clearance of total inhibitor
- Vx: central volume of inhibitor
- Vx_{slow}: volume of slow equilibrating inhibitor compartment
- Qx_{slow}: distributional clearance of slow equilibrating inhibitor compartment
- Vx_{fast}: volume of fast equilibrating inhibitor compartment
- Qx_{fast}: distributional clearance of fast equilibrating inhibitor compartment
- Ka: absorption rate of inhibitor
- Tlag: lag time of inhibitor absorption
- Fup: fraction of unbound inhibitor from plasma protein
- Kd: dissociation constant of inhibitor – andexanet complex (koff/kon)
- Xabs: absorption of inhibitor
- QX_{seq}: rate of free inhibitor return from sequestration
- Prot: plasma proteins, other than andexanet

Objective

- The goal of this analysis was to validate the PK/PD models of andexanet with apixaban and rivaroxaban. Model-predicted anti-FXa activity reversal was compared to observed reversal in healthy subjects administered andexanet in the presence of steady state levels of apixaban or rivaroxaban.

Methods

- Data from a phase 1 study (16-512) of healthy subjects anticoagulated with apixaban or rivaroxaban and administered andexanet were used to externally validate the PK/PD models.
- Time courses of anti-FXa activity and percent reduction from pre-andexanet levels were simulated for each individual in the apixaban and rivaroxaban cohorts and compared with observed data.
- In the second approach to validation, previous PK/PD datasets were expanded to include the additional Phase 1 data and models re-run to fit the expanded datasets. New parameter estimates were compared with the original results.

Results

- Plasma samples from 72 subjects (apixaban, n = 41; rivaroxaban, n = 31) in Study 16-512 were available for comparisons with the refined PK/PD model.
- For rivaroxaban, mean percent reversal of anti-FXa activity observed was similar to that predicted by the PK/PD model (**Table 2**).
- Similarly for apixaban, mean percent reversal of anti-FXa activity observed was similar to that predicted by the PK/PD model (**Table 3**).
- Changes in PK/PD model parameters with the new data were generally small. The largest changes were in the slow compartment distributional clearance (QX) for rivaroxaban and the dissociation constant (Kd) for apixaban **(Table 4)**. Sensitivity analyses showed limited impact of the differences.

Table 2. Validation of Andexanet-rivaroxaban PK/PD Model

Protocol Time	n	Observed % Reversal		Predicted % Reversal	
		Median	90% CI	**Median**	90% CI
End of bolus (EOB)	30	**94.3**	89.7, 97.1	**92.4**	66.8, 97.6
End of infusion (EOI)	31	**95.1**	81.4, 98.0	**91.6**	67.1, 98.4
1.5 hours post EOI	31	**55.2**	-6.4, 77.2	**60.4**	14.8, 88.5
5.5 hours post EOI	31	**57.7**	30.8, 71.9	**57.9**	29.4, 71.8
8.5 hours post EOI	31	**68.6**	52.3, 80.5	**72.1**	51.1, 82.6

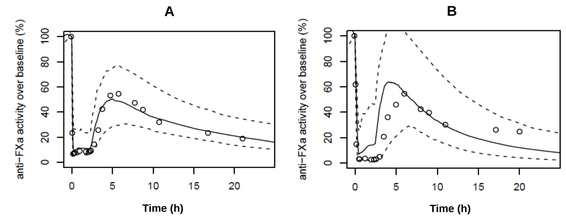
Table 3. Validation of Andexanet-apixaban PK/PD Model

Protocol Time	n	Observed % Reversal		Predicted % Reversal	
		Median	90% CI	**Median**	90% CI
EOB	40	**92.2**	89.2, 97.0	**92.0**	79.7, 96.8
EOI	40	**91.4**	85.2, 97.6	**88.9**	76.6, 97.7
1.5 hours post EOI	41	**61.8**	42.7, 88.7	**58.0**	36.9, 88.8
5.5 hours post EOI	41	**54.7**	39.8, 62.9	**53.6**	26.0, 74.3
8.5 hours post EOI	42	**63.4**	50.3, 75.2	**61.4**	40.9, 78.6

Table 4. Relative Changes in Andexanet-rivaroxaban and Andexanet-apixaban PK/PD Model (Expanded Data Versus Base Data)

Parameter	Rivaroxaban Relative Change	Apixaban Relative Change
FXa Inhibitor central clearance: CLx (L/h)	-3%	-8%
FXa inhibitor central volume: Vx (L)	-17%	21%
FXa inhibitor slow distributional clearance: Qx (L/h)	48%	-12%
FXa inhibitor slow equilibrating tissue volume: Vxp (L)	2%	-4%
FXa inhibitor absorption rate: Ka (/h)	0%	15%
Lag time in FXa inhibitor absorption: Tlag (h)	-1%	-10%
Fraction unbound of FXa inhibitor from plasma protein: Fu	1%	1%
Binding dissociation constant between andexanet and FXa inhibitor: Kd (μM)	5%	25%
Slope on free rivaroxaban to anti-FXa activity: SL	6%	-3%
FXa inhibitor fast equilibrating tissue volume: VXD (L)	-21%	11%
Rate of free FXa inhibitor return from sequestration: QRE (/h)	0%	-1%
Rate of bound andexanet-FXa inhibitor to sequestration: CLB (L/h)	-10%	-16%
Rivaroxaban slope of LBM effect on CLX: SLLBMCL	-7%	NA
Apixaban central clearance, non-renal component : CLXNR (L/h)	NA	6%

Figure 2. Examples of Individual Subject Anti-FXa Activity Divided by Baseline (%) for Apixaban (A) and Rivaroxaban (B) Versus Model Predicted With 90%CI



Conclusions

- The refined PK/PD models in healthy subjects that had been adjusted for covariates specific for patient populations taking FXa inhibitors closely predicted the level of anticoagulation reversal observed in a new study of healthy subjects, validating the PK/PD models for andexanet with apixaban or rivaroxaban.
- The predictions were within the 90% CIs for rivaroxaban and apixaban through 8 hours after the end of infusion. 98% of apixaban and 90% of rivaroxaban data points were within the 90% CI (**Figure 2**).
- Model parameters with and without the new data were very close, providing further evidence of the validity of the PK/PD models.

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