

# Office of Clinical Pharmacology Review

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<b>NDA or BLA Number</b>	BLA 125586/0
<b>Link to EDR</b>	\\cber-fs3\m\ectd_submissions\BLA125586
<b>Submission Date</b>	December 17, 2015
<b>Submission Type</b>	Priority review; Consult review
<b>Brand Name</b>	Andexxa®
<b>Generic Name</b>	Andexanet alfa
<b>Dosage Form and Strength</b>	Lyophilized powder for solution for intravenous injection: 100 mg in a single-use vial
<b>Route of Administration</b>	Intravenous injection
<b>Proposed Indication</b>	<p>For patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed in situations such as:</p> <ul style="list-style-type: none"> <li>• In life-threatening or uncontrolled bleeding</li> <li>• (b) (4)</li> </ul>
<b>Applicant</b>	Portola Pharmaceuticals, Inc.
<b>Associated IND</b>	IND 15089
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## 1. EXECUTIVE SUMMARY

The Applicant submitted original BLA 125586 for Andexxa® (andexanet alfa) on December 17<sup>th</sup>, 2015. Andexanet alfa is a recombinant factor Xa protein that has been developed as a universal reversal agent for direct factor Xa inhibitor (apixaban, edoxaban, rivaroxaban) and indirect factor Xa inhibitor (low molecular weight heparins such as enoxaparin) anticoagulants. Andexanet alfa has been truncated and modified so that is catalytically inactive with regards to activating prothrombin. Andexanet alfa's mechanism of action is that it serves as an alternative binding site for direct and indirect factor Xa inhibitors in the blood, freeing up endogenous factor Xa. The applicants proposed dosing regimens, classified based on 'low' and high' dose and further classified by factor Xa inhibitor and time since last dose are shown below in **Table 1** and **Table 2**.

**Table 1. Andexanet Alfa Dosing Regimens**

Dose	Initial IV Bolus	Follow-On IV Infusion
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for up to 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for up to 120 minutes

**Table 2. Andexanet Alfa Recommended Dosage**

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose Before Andexanet Alfa Initiation	
		< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	:S 10 mg	Low Dose	Low Dose
	> 10 mg / Unknown	High Dose	
Apixaban	:S 5 mg	Low Dose	
	> 5 mg / Unknown	High Dose	
(b) (4)			

In the current submission, the Office of Clinical Pharmacology was asked to provide comments on consult questions received from the Division of Hematology Clinical Review (see section 3.3), Office of Blood Review and Research in the Center for Biologics Evaluation and Research.

The key review findings with comments are summarized below:

<b>Review issues</b>	<b>Comments</b>
<b>Evidence of effectiveness</b>	Pharmacokinetic and pharmacodynamic evaluation in healthy volunteers administered apixaban or rivaroxaban provided evidence of effect and supports the mechanism of action for reversal of the anticoagulant effects of the factor Xa inhibitors.
<b>General dosing instructions</b>	<p>The proposed dosing is excessively complicated and may be difficult to implement clinically.</p> <p>The review team proposes a simplification of dosing to use the highest bolus and maintenance dose (800 mg followed by 8 mg/min over 2-h) in all patients regardless of whether the patient is on rivaroxaban or apixaban or time since last dose.</p> <p>The evaluated infusion duration of 2-hours is not sufficient, and longer infusion durations may be needed in patients. See Section 2.3 for (Outstanding Issues) for more information.</p>
<b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>	Dedicated pre-market studies of andexanet alfa in subjects to explore different intrinsic factors (specifically renal impairment) are not required. An option for tailoring the duration of infusion based on patient response may be a more effective approach.

## **2.SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT**

### **2.1 Pharmacology and Clinical Pharmacokinetics**

#### **Pharmacokinetics of andexanet alfa**

- Andexanet alfa exhibits linear pharmacokinetics over a bolus dose range of 30 to 800 mg. Pharmacokinetics remained linear with use of a 2-h infusion at up to 8 mg/min.
- Andexanet alfa has a clearance of 4.3 L/h and a volume of distribution of 5 L based on population PK analyses.
- Andexanet alfa, achieves peak exposures following bolus administration of the proposed dose. Andexanet alfa exposure gradually decreases over the maintenance infusion duration. Andexanet alfa is rapidly eliminated from the system and is <5% of post-bolus concentration 2-3 h after the end of the infusion. Andexanet alfa can be detected out to 24-h at low levels (i.e., <0.1 µg/mL).

- The impact of age, sex, race, body weight, or renal function on andexanet alfa exposure was not evaluated during this consult. Nonclinical studies indicated that up to 50% of andexanet alfa is eliminated renally; the impact of renal function was not evaluated clinically.

### **Pharmacodynamics of andexanet alfa**

- Unbound factor Xa inhibitor concentration decreases immediately following andexanet alfa administration, and suppression of unbound factor Xa inhibitor concentration is maintained throughout the infusion. Concurrent with the decrease in unbound factor Xa inhibitor concentration, there is a decrease in anti-factor Xa levels. Anti-factor Xa levels, rather than being a direct measure of anticoagulation, may more appropriately reflect unbound factor Xa inhibitor concentrations.
- Total factor Xa inhibitor drugs levels (bound + unbound) increase following administration of andexanet alfa due to sequestering of the factor Xa inhibitor from peripheral tissue and the system reaching a new equilibrium.
- Following the end of andexanet alfa infusion, unbound factor Xa inhibitor concentrations increase with a corresponding increase in anti-factor Xa.
- This restoration of anticoagulation can be attributed to andexanet alfa pharmacokinetics as it is eliminated from the systemic circulation.
- Unbound factor Xa inhibitor concentration and anti-factor Xa levels following the end of infusion exceed levels in corresponding placebo cohorts. This ‘rebound’ can be explained by:
  - i) sequestration of drug from peripheral tissue.
  - ii) higher total drug concentrations in the systemic circulation during the andexanet alfa infusion.
  - iii) reestablishment of protein binding equilibrium once andexanet alfa has been substantially eliminated from the system.
- Of the pharmacodynamic markers for coagulation that were collected and evaluated (prothrombin time, activated partial thromboplastin time, activated coagulation time, and endogenous thrombin generation [PT, APTT, ACT, ETP]) ACT best mirrors unbound drug concentration (and anti-factor Xa levels).
- ACT decreases following andexanet alfa administration to values representative of baseline ACT. Consequently, ACT values increase when the infusion is stopped coinciding with the observed increases in unbound factor Xa inhibitor concentration. ACT may be a reasonable coagulation marker for monitoring reversal.
- ETP is also correlated with unbound factor Xa inhibitor concentrations, with lower ETP values corresponding to higher factor Xa inhibitor concentrations. Following administration of andexanet alfa, ETP levels increase above baseline, where it is maintained through the infusion duration. Following the end of the infusion, ETP levels decrease to within typical baseline values. Compared to placebo cohorts (subjects

administered a factor Xa inhibitor and placebo ‘andexanet alfa’), ETP levels remain elevated 2-3 h after the end of the infusion suggesting that administration of andexanet alfa alters the factor Xa inhibitor-ETP relationship. Elevated ETP levels are maintained out to 48 h. This observation is conceptually similar to changes in ETP observed following administration of prothrombin complex concentrates (PCC) in healthy volunteers on apixaban (Labeling Supplement Review by Dr. Ju-Ping Lai on February 26<sup>th</sup>, 2016 [Reference ID: 3893388]) or rivaroxaban (Supplement NDA Review by Dr. Joseph Grillo on November 27<sup>th</sup>, 2013 [Reference ID: 3414340]).

- Andexanet alfa has off-target coagulation effects mediated by its interaction with tissue factor pathway inhibitor (TFPI). Administration of andexanet alfa was associated with decreases in free TFPI and total TFPI that persisted for 48-72 h. D-dimer levels were increased following andexanet alfa administration with a majority (65-91% and 35-57%) of subjects having D-dimer levels >ULN at 24 and 48 h after andexanet alfa administration, respectively.

## **2.2 Dosing and Therapeutic Individualization**

### **2.2.1 General dosing**

The general dosing proposed by the Applicant in **Table 1** and **Table 2** is excessively complicated and could be simplified. Based on the available information, the OCP Review Team believes that pragmatic dosing can be provided for apixaban and rivaroxaban. Rather than tailoring andexanet alfa dose based on factor Xa inhibitor and time since last factor Xa inhibitor dose, the high dose (800 mg as a bolus followed by an 8 mg/min infusion) could be administered to all patients. This dose was studied in healthy volunteers on background of rivaroxaban and provides some empirical safety coverage for use with apixaban. The use of a single bolus and maintenance dose would also reduce the potential for under-dosing based on incorrect information provided by the patient at the time treatment is initiated (i.e., incorrect reporting of time from last dose). Finally, the use of the highest safe dose in all patients is similar to the dose selection utilized for idarucizumab, a reversal agent for dabigatran.

### **2.2.2 Therapeutic individualization**

Given the proposed indication, the bolus and maintenance portions of the dosing regimen should be administered at as high a dose as safety data permits. However, the duration of the infusion could be tailored based on patient response. For example, it may not be necessary to continue the infusion beyond when the bleeding is stopped. Similarly, it may be beneficial to maintain the infusion beyond 2-h if the bleeding event has not yet resolved. Labeling could be included to permit clinicians with sufficient flexibility to maintain the infusion for longer durations or to re-administer andexanet alfa if bleeding persist or recurs. Additional clinical data may be necessary to support extending the infusion duration or to permit retreatment.

## 2.3 Outstanding Issues

Inhibition of factor Xa and corresponding anticoagulant effect was restored to some extent 2 to 3 h following the end of the andexanet alfa infusion based on global markers of anticoagulation, such as ACT. In addition, a 2 h limit on the infusion duration may be insufficient if bleeding persist or recurs in patients. Both of these issues could be mitigated with longer andexanet alfa infusion duration. There is adequate pharmacokinetic and pharmacodynamic data available to inform the infusion duration based on data that has already been collected. However, the datasets and the analysis programs for the PK/PD modeling report (qsandexanet001.pdf) have not been submitted. These materials could be used to further optimize the duration of infusion. Additional safety data may also be needed to support longer infusion duration.

Another outstanding issue is the potential consequence of the off-target effects of andexanet as manifested by the effects on TFPI, D-dimer, and prothrombin fragment 1 and 2. Elevated D-dimer levels have been implicated as a potential risk factor for recurrence of DVTs (Kearon, Chest 2012). In addition, suppression of TFPI with oral contraceptive use is one of the proposed mechanisms for an increased risk of deep venous thrombosis with those drugs (Harris, Am J Hematol 1999). The clinical consequences of these alterations in TFPI and D-dimer levels under the current context (i.e., elevations up to 72 h) are not clear and designing dedicated efficacy and safety studies to understand the clinical impact of changes in these measures is not practical.

Any additional studies that are conducted should include comprehensive collection of andexanet alfa concentration, unbound and total factor Xa inhibitor concentration, anti-factor Xa levels, global coagulation markers, and other pharmacodynamic markers such as free and total TFPI, D-dimer, and prothrombin fragment 1 and 2.

The comments in this consult review predominantly focus on the use of andexanet alfa with apixaban and rivaroxaban. However, there is utility in having andexanet alfa available as a treatment option for indirect factor Xa inhibitors and other direct factor Xa inhibitors such as edoxaban. In order to support dosing for edoxaban, the data sets from the completed healthy volunteer study should be provided, including unbound edoxaban concentrations. Based on protein binding and volume of distribution for edoxaban, higher andexanet alfa doses may be needed to suppress unbound edoxaban concentrations. A complete review of the enoxaparin information could not be completed during this consult. Similar analyses to those conducted for apixaban and rivaroxaban should be provided to support dosing of andexanet alfa with enoxaparin. Alternatively, as an andexanet alfa maintenance infusion was not administered in the enoxaparin study (only bolus administration), the Applicant could include a cohort of patients on enoxaparin in studies evaluating a longer infusion duration.

### 3.COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

#### 3.1 Overview of the Product and Regulatory Background

Currently, there are no approved reversal agents for factor Xa inhibitors. Idarucizumab is a recently approved reversal agent for dabigatran, but it cannot reverse the activity of direct or indirect factor Xa inhibitors. The rivaroxaban label includes information regarding partial reversal of prothrombin time prolongation after administration of PCCs but is not an approved intervention for this indication. A short summary of the drug properties, effect on pharmacodynamic markers, and labeling for idarucizumab and andexanet alfa are provided below in [Table 3](#).

**Table 3. A Comparison between Andexanet Alfa and Idarucizumab Drug Properties, Pharmacodynamics, and Labeling**

	<b>Andexanet alfa</b>	<b>Idarucizumab</b>
<b>Molecular Entity</b>	Recombinant factor Xa protein	Humanized monoclonal antibody fragment
<b>Binds with the following anticoagulants</b>	Direct and indirect fXa inhibitors	Dabigatran
<b>Initial half-life</b>	(b) (4)	~50 minutes
<b>Route of elimination</b>	Not assessed. Animal data support renal elimination may substantially contribute.	Elimination reduced in patient with impaired renal function. No dose reductions recommended
<b>How is it administered</b>	Bolus followed by maintenance infusion	Two consecutive short duration infusions
<b>Half-life of drug/anticoagulant complex</b>	(b) (4)	(b) (4)
<b>Coagulation tests that correlate with anticoagulant effect</b>	(b) (4)	Diluted thrombin time; ecarin clotting time
<b>Off-target effects of the reversal agent</b>	Decreases free TFPI, and total TFPI; increases D-dimer	None identified from submission
<b>Re-dosing permitted in labeling</b>	Proposed label does not mention: i) re-dosing, what to do if bleeding continues beyond 2 h, or how to handle recurrence of elevated coagulation parameters following end of the infusion	Additional 5 g may be considered in patients with clinically relevant bleeding and with elevated coagulation parameters
<b>Rebound in anticoagulation after administration</b>	2-3 h after end of infusion; almost all subjects	Subset of subjects 12 to 24 hours after administration



The andexanet alfa development program included the following studies providing clinical and clinical pharmacology data to support the proposed indication:

- Study 11-501: safety and pharmacokinetic Phase 1 study (healthy subjects) dosed with andexanet alfa alone.
- Study 14-506: pharmacokinetic (PK) and pharmacodynamics (PD) Phase 1 study comparing elderly (65 years and older) and younger (18 to 45 years) healthy subjects dosed with andexanet alfa in the presence of apixaban.
- Study 12-502: dose-ranging Phase 2 study of healthy subjects dosed with andexanet in the presence of various factor Xa inhibitors (apixaban, rivaroxaban, enoxaparin and edoxaban).
- Study 14-503: double-blind, placebo-controlled Phase 3 study of andexanet alfa in the presence apixaban in healthy subjects (50 to 75 years old)
- Study 14-504: double-blind, placebo-controlled Phase 3 study of andexanet alfa in the presence of rivaroxaban in healthy subjects (50 to 75 years old)
- Phase 3b/4 ANNEX-4 study (14-505): a multicenter, prospective, open-label single-arm study of andexanet alfa in approximately 250 subjects with acute major bleeding who have recently received apixaban, rivaroxaban, edoxaban or enoxaparin
  - Data from 35 subjects enrolled in the confirmatory at the time of submission.
  - Updated information, including 57 patients, was provided by the Applicant on June 17<sup>th</sup>, 2016. This update was not reviewed as part of this consult.

### 3.2 General Pharmacological and Pharmacokinetic Characteristics

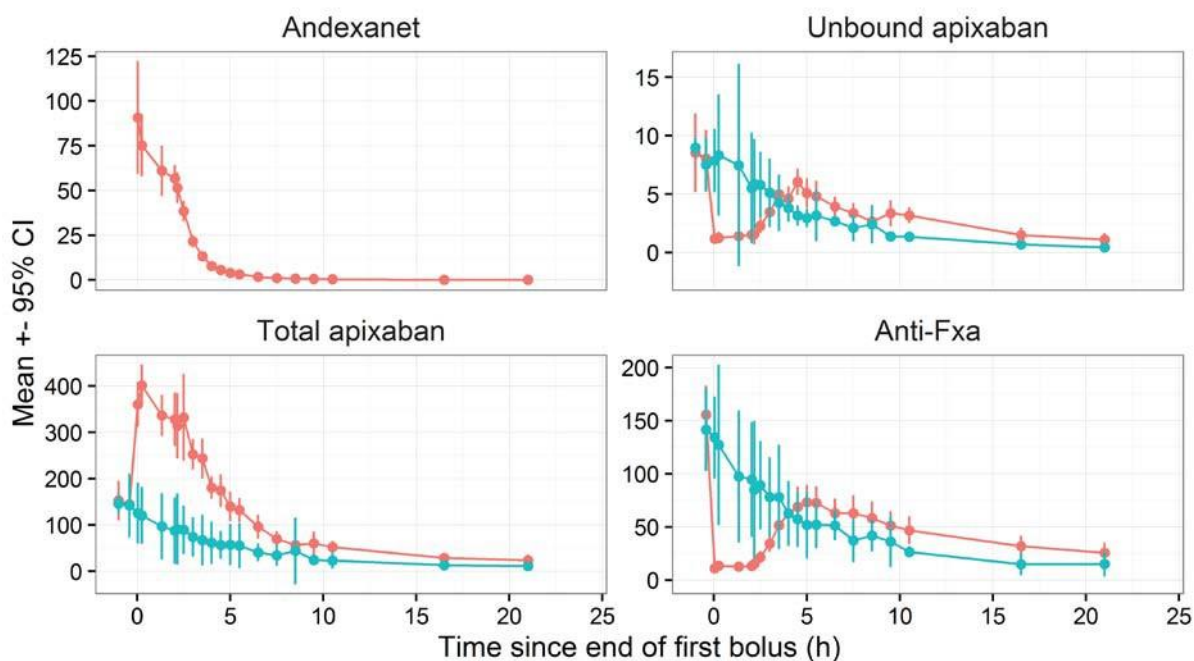
Andexanet alfa is a recombinant modified version of human factor Xa protein. It is proposed to have no pro- or anti-coagulant activity and has a molecular weight of ~41 kDa.

#### General PK properties

Andexanet alfa PK were assessed in a single ascending dose study (11-501) in younger and older subjects (14-506) as well as two dose ranging PK/PD studies in the presence of an anticoagulant (12-501m1: apixaban) and (12-502m2: rivaroxaban). The time-profile for andexanet alfa PK for the highest dose cohort (420 mg and 4 mg/min over 2 h) in the presence of apixaban is shown in **Figure 1** in the top left panel. This figure shows the decline of andexanet alfa concentrations during the infusion, which was observed at all infusion rates. Furthermore, the figure illustrates the rapid elimination of andexanet alfa (b) (4) half-life) as the andexanet alfa plasma concentration is <5% of the maximum concentration (b) (4) after the end of infusion (~5 hour since the end of the first bolus). Andexanet alfa plasma concentration levels are detectable out to at least 24 h at < 0.1 µg/mL due to a prolonged terminal elimination phase. Following administration of andexanet alfa there is a direct effect on unbound fXa inhibitor and anti-factor Xa (right panels) and mobilization of factor Xa inhibitor from peripheral tissue (lower left).

Andexanet alfa has a clearance of ~4.3 L/h and a volume of distribution of ~5 L based on population PK analysis and exhibits linear pharmacokinetics in the studied range (30 to 800 mg

bolus; see [Table 4](#)). The pharmacokinetics of andexanet is not influenced by coadministration with apixaban or rivaroxaban.



**Figure 1** Time course of andexanet PK (top left), total apixaban (bottom left), unbound apixaban (top right) and anti-factor Xa levels (bottom right) from cohort 6 (400 mg bolus + 4 mg/min over 2 h). (*Data source: Study 12-502 [module 1, cohort 6]*)

**Table 4.** Andexanet PK parameters following bolus IV administrations of 30, 90, 300, 600 mg (11-501), and bolus/maintenance IV administration of 420 mg and 4 mg/min (12-502m1) and 800 mg / 8 mg/min for 2 h (12-502m2). (*Data source: studies 11-501, 12-502 [module 1] and 12-502 [module 2]*).

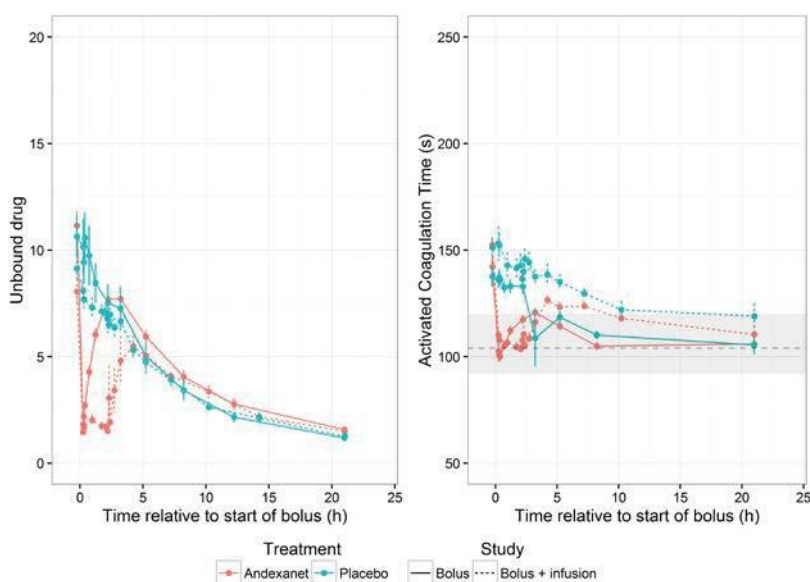
Dosing regimen	Study		Cmax (µg/mL)
30 mg	11-501	N	6
		Mean±SD	3.1±0.4
90 mg	11-501	N	6
		Mean±SD	10.8±4.1
300 mg	11-501	N	6
		Mean±SD	52.8±13.1
420 mg 4 mg /min	12- 502m1	N	6
		Mean±SD	90.1±29.6
600 mg	11-501	N	6
		Mean±SD	93.3±14.2
800 mg 8 mg/min	12- 502m2	N	6
		Mean±SD	161±40.4

Preclinical experiments show a potential for renal elimination of andexanet alfa. Specifically the clearance of andexanet alfa was decreased by 29% and 51% in unilateral and bilateral nephrectomized rats. It may be reasonable to expect contribution of renal pathway to the overall elimination of andexanet alfa, as it is biologic with molecular weight less than 69 kDa

(Pharmacokinetics in Patients with Impaired Renal Function, FDA Guidance 2010). However, the impact of renal impairment on elimination of andexanet alfa was not evaluated clinically. Limited experience does exist for the impact of age on andexanet elimination. In a small dedicated study comparing PK of andexanet alfa in healthy younger and older subjects (14-506), there were no differences between the two age groups in PK.

### General PD properties

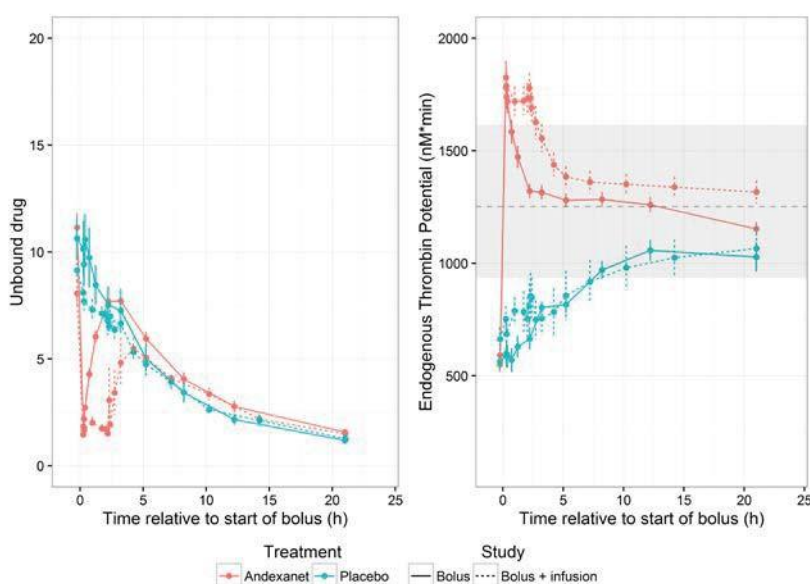
Administration of andexanet alfa results in an immediate suppression of unbound factor Xa inhibitor concentrations and anti-factor Xa levels (**Figure 1**). However, anti-factor Xa levels are considered to be a measure of unbound factor Xa inhibitor concentrations and do not necessarily reflect changes in coagulation. Therefore, multiple coagulation markers, such as PT, APTT, ACT and ETP, were evaluated to assess the ability of andexanet alfa to restore coagulation. For ease, only the impact of andexanet on the anticoagulant effect of apixaban is presented below. Similar effects were also noted with rivaroxaban and are presented later in the document. Of the evaluated coagulation markers, ACT tracked changes in unbound apixaban (and rivaroxaban), showed a return to baseline levels after administration of andexanet alfa (**Figure 2**), and appears to be a reasonable coagulation marker for monitoring reversal of apixiban and rivaroxaban anticoagulation effects.



**Figure 2** Time course of unbound apixaban (left) and activated coagulation time (right) for subjects receiving apixaban and andexanet (red) and apixaban and placebo (teal). The solid lines refer to bolus (400 mg) of andexanet or placebo and the dashed line refers to bolus and a 2 h infusion (4 mg/min). The dashed line and shaded area represents the 5<sup>th</sup> to 95<sup>th</sup> percentile of baseline values (shaded area) or median baseline (dashed line). (*Data source: Study 14-503*)

ETP is also correlated with unbound factor Xa inhibitor concentrations but less sensitive compared to ACT (**Figure 3**). Interestingly, an overshoot in ETP levels is observed during andexanet alfa infusion and slightly elevated ETP levels persists out to 48 h post andexanet alfa

administration. This degree of overshoot above baseline in ETP levels has also been observed following administration of prothrombin complex concentrates (PCCs) to subjects on apixaban or rivaroxaban. In healthy volunteer studies, subjects administered PCCs had an increase in ETP above baseline values that persisted for 48 to 72 h following administration. Unlike andexanet alfa the elevation in ETP levels with PCCs was not immediate. ETP levels gradually increase with maximum levels observed around 24 h after administration. The elevation in ETP observed following PCCs administration is likely a result of infusing the system with high concentrations of human coagulation factors (e.g., factor II, VII, IX, and X). In contrast, the slight elevation and overshoot in ETP for andexanet alfa can potentially be explained by binding of andexanet alfa with TFPI.



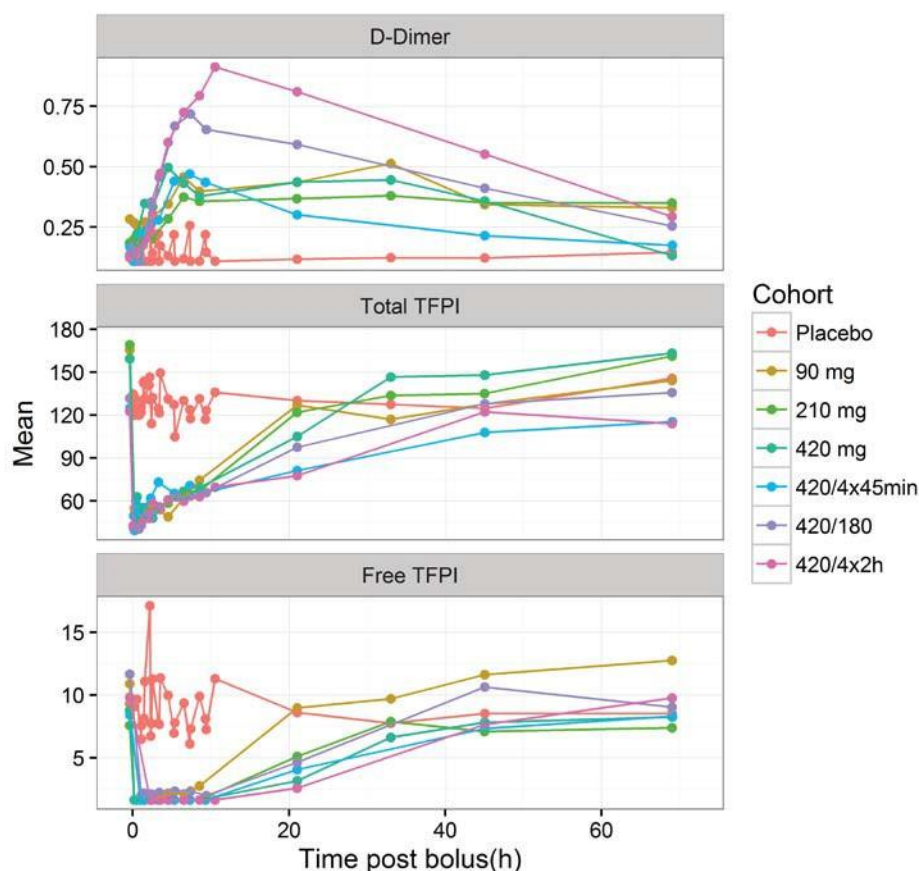
**Figure 3** Time course of unbound apixaban (left) and endogenous thrombin potential (right) for subjects receiving apixaban and andexanet (red) and apixaban and placebo (teal). The solid lines refer to bolus (400 mg) of andexanet or placebo and the dashed line refers to bolus and a 2 h infusion (4 mg/min). The dashed line and shaded area represents the 5<sup>th</sup> to 95<sup>th</sup> percentile of baseline values (shaded area) or median baseline (dashed line). (*Data source: Study 14-503*)

#### Off-target PD effects

**Figure 4** shows that andexanet alfa decreases both total and free TFPI and increases D-dimer in a dose-dependent manner. Both changes in TFPI and D-dimer last longer than the effects on anti-factor Xa levels. The changes in TFPI has been hypothesized to result from andexanet binding to TFPI on the Kunitz 2 domain (same as factor Xa), which explains why free TFPI levels remain low for 24-48 h as Kunitz interactions are slow and tight (Broze, Front Biosci 2012). Increases in D-dimer were also observed in the andexanet alfa single ascending dose study (11-501) in the absence of an on board factor Xa inhibitor. Interestingly the changes in D-dimer were greater than the changes observed with a factor Xa inhibitor on board.

It is worth noting that from review of the assay reports of total TFPI (CQ-12-4-002-r6-a1) and free TFPI (CQ-12-4-002-r5-a1), it is not clear what exactly is measured by total and free TFPI. In particular, some free TFPI assays use antigen that binds to the Kunitz 3 domain of TFPI, which is unique to one form of TFPI (TFPIa) and no other active forms of TFPI, such as TFPI $\beta$  (Broze, Front Biosci 2012). The Applicant provided responses in an information request (Seq 39, 1113-m1-ax-00111rd) regarding the assay but this material could not be completely reviewed during this consult. Further clarification about what was measured with these two assays should be requested. However, even if the assay measured only a specific form of TFPI the results across the healthy volunteer studies support that levels of TFPI are decreased. The clinical implications of the interaction between andexanet alfa and TFPI are not known.

If longer infusion duration is evaluated, the study should include collection of coagulation markers (such as ACT and ETP) as well as D-dimer and TFPI levels to determine if there is any further impact on TFPI resulting from longer infusion duration.



**Figure 4** Time course of D-dimer (top), total TFPI (middle) and free TFPI (bottom) for subjects in study 12-502m1 (*Data source: Study 12-502 [module 1]*)

### 3.3 Clinical Pharmacology Consult Questions

In healthy subjects who received rivaroxaban, apixaban and edoxaban, a decline in anti-FXa activity was observed during and for a short duration following the end of the andexanet infusion. For rivaroxaban and apixaban this decline was subsequently followed by a rebound of anti-FXa activity levels; for high dose rivaroxaban this rebound resulted in anti-FXa activity levels that were higher than placebo. Furthermore, even during infusion treatment with andexanet did not result in complete reversal. For example, in subjects anticoagulated with edoxaban, anti-FXa levels of up to 50 ng/mL are observed after reversal with andexanet. For each of the aforementioned anticoagulants, please comment on:

a) The adequacy of the depth of reversal, as evidenced by reduction in anti-FXa activity and unbound anticoagulant. Considering the PK/PD parameters of each anticoagulant and of andexanet, are the observed decreases in anti-FXa activity and unbound anticoagulant as expected?

#### Adequacy of depth of reversal:

Unbound factor Xa inhibitor concentration and anti-factor Xa levels following the proposed bolus and maintenance doses of andexanet alfa are substantially decreased compared to pre-andexanet alfa levels. Unbound factor Xa inhibitor concentrations and anti-factor Xa levels observed are comparable to values that would typically be observed 48 h after the last dose of apixaban or rivaroxaban (see [Table 5](#)). This information suggests that the depth of reversal is adequate.

**Table 5.** Comparison of the inter-quartile range for the unbound drug and anti-FXa levels at pre-andexanet, nadir following andexanet and 48 hours after the last dose of apixaban or rivaroxaban in the placebo. (Data source: Study 12-502 [modules 1 & 2])

Metric	Apixaban (ng/mL)			Rivaroxaban (ng/mL)		
	Nadir (andexanet)	Pre- andexanet	48 h post- dose (Placebo)	Nadir (andexanet)	Pre- andexanet	48 h post- dose (Placebo)
Unbound factor Xa inhibitor	1.1 (0.9 – 1.2)	8.6 (7.2 – 10.1)	0.3 (0.3 – 0.5)	4.8 (2.3 – 5.2)	22.6 (17.8 – 28.2)	0.5 (0.4 – 0.5)
Anti-FXa	11.3 (9.2 – 12.5)	161.6 (146.5 – 180.5)	3.9 (2.4 – 6.6)	16.3 (8.6 – 18.8)	228.8 (164.4 – 250.0)	4.0 (1.4 – 7.0)

*Note: The recommendations for surgery in practice guidelines for apixaban and rivaroxaban is to wait 48 – 72 hours after the last dose.*

#### Adequacy of apixaban and rivaroxaban exposure in the current program:

The observed steady state drug concentrations in the healthy volunteer studies for rivaroxaban and apixaban are comparable to concentrations observed in the Phase 3 registration trials for these drugs ([Table 6](#)).



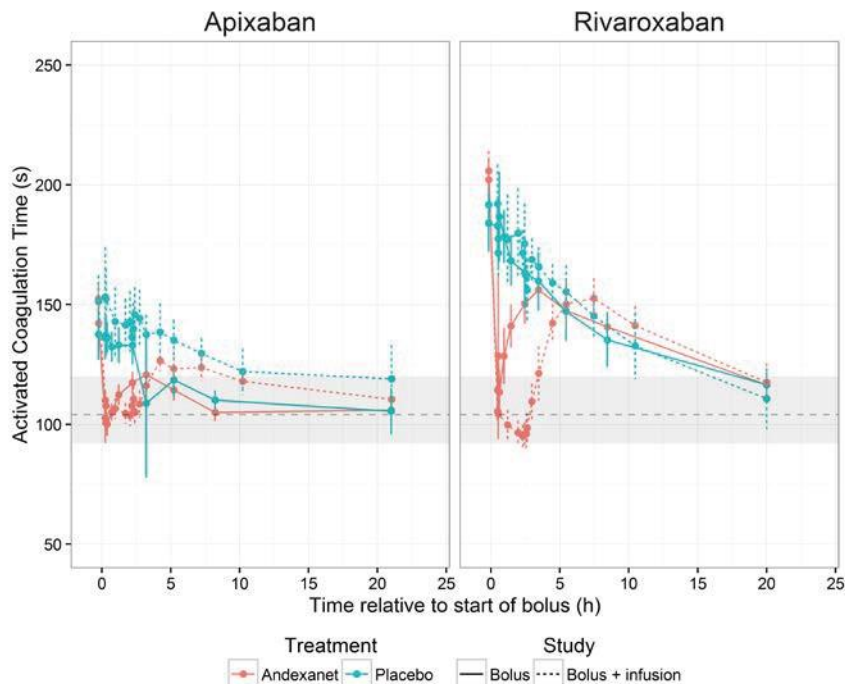
**Table 6.** Comparison of the steady-state exposures for apixaban and rivaroxaban across different development programs (Note: Median or 5th – 95th percentiles presented) (*Data source: Study 12-502 [modules 1 & 2]*)

Source	Apixaban (ng/mL)		Rivaroxaban (ng/mL)	
	Ctrough	Cmax	Ctrough	Cmax
<b>Andexanet program</b>	36 - 77	108-222	10-35	201-404
<b>DVT<sup>#</sup></b>	63	132	19-60	175-360
<b>Atrial fibrillation<sup>#</sup></b>	41 – 230*	91 – 321*	4-96	160-360

\*Predicted steady-state exposure

<sup>#</sup>Information obtained from: <http://thrombosisjournal.biomedcentral.com/articles/10.1186/1477-9560-11-11> and <https://depts.washington.edu/anticoag/home/content/uw-medicine-alternative-monitoring-antithrombotic-agents>

Furthermore, the available PK and PD data suggests that the depth of reversal represents a reasonable restoration of normal hemostasis over the duration of treatment with andexanet alfa. For example the time course of ACT show immediate normalization to baseline levels following bolus and over the duration of andexanet maintenance infusion. Similar observations are noted for PT and ETP, however, ACT appears to be a more sensitive marker.



**Figure 5** Time course of ACT, for apixaban (left) and rivaroxaban (right) following the administration of andexanet (Red) or Placebo (Blue) at steady-state Cmax following 3 days of administration of apixaban 5 mg BID or rivaroxaban 20 mg QD. Note: The time course is truncated to 24 hours for ease of presentation. (*Data source: studies 14-503 and 14-504*)

Additional observations:

- 1) There is a clear relationship between andexanet dose and unbound factor Xa inhibitor (or anti-factor Xa) nadir over a range of cohorts administered andexanet alfa as a bolus in 12-502 module 1 and 2. Based on observations from 12-502 (module 1 and 2), the proposed bolus and magnitude of the maintenance dosing appears sufficient and is further confirmed in 14-503 and 14-504.
- 2) A need for an a higher bolus dose and higher maintenance dose for rivaroxaban can be explained based on protein binding, drug concentrations at steady state, and volume of distribution.

**b) The potential adequacy of the observed duration of reversal, given the fact that the T1/2 of the anticoagulants as a group are on the order of 10 hours.**

The duration of infusion does not appear to be sufficient. In studies 12-502, 14-503, and 14-504, an immediate and sustained suppression of anti-factor Xa, unbound factor Xa inhibitor concentrations, and various anticoagulant biomarkers result from the selected bolus and infusion duration. However, following cessation of the infusion, there is a rebound in anti-factor Xa activity and unbound factor Xa inhibitor concentration (see response 'c' also). This rebound is of sufficient magnitude that it exceeds values observed 48-72 hours after cessation of treatment, a recommendation for stopping apixaban and rivaroxaban therapy prior to surgery. As such, the rebound would reflect a change in coagulation that may be of clinical relevance.

Based on the available data, the rebound can be prevented or mitigated with longer andexanet alfa infusion. This observation is supported by observations from study 12-502. Comparison of the unbound factor Xa inhibitor concentrations and anti-factor Xa levels following administration of andexanet alfa as a bolus or as a bolus with infusion show that the timing of the rebound is pushed further out in time by including a maintenance infusion.

There is sufficient information available in the provided modules to inform how the duration of infusion should be extended to avoid a rebound exceeding various thresholds based on timing of the last dose. Dosing recommendations regarding the duration of infusion could be developed by combining this information with the modeling report provided by the Applicant. Further, we would advise the Applicant to conduct additional simulation exercises based on the submitted modeling report.

**c) Possible mechanisms for the observed rebound of anti-fXa activity in subjects anticoagulated with apixaban and rivaroxaban and the apparent absence of rebound for edoxaban. Are these differences explained in part by differences in PK/PD parameters? Could they be explained by mobilization of anticoagulant from extravascular locations?**

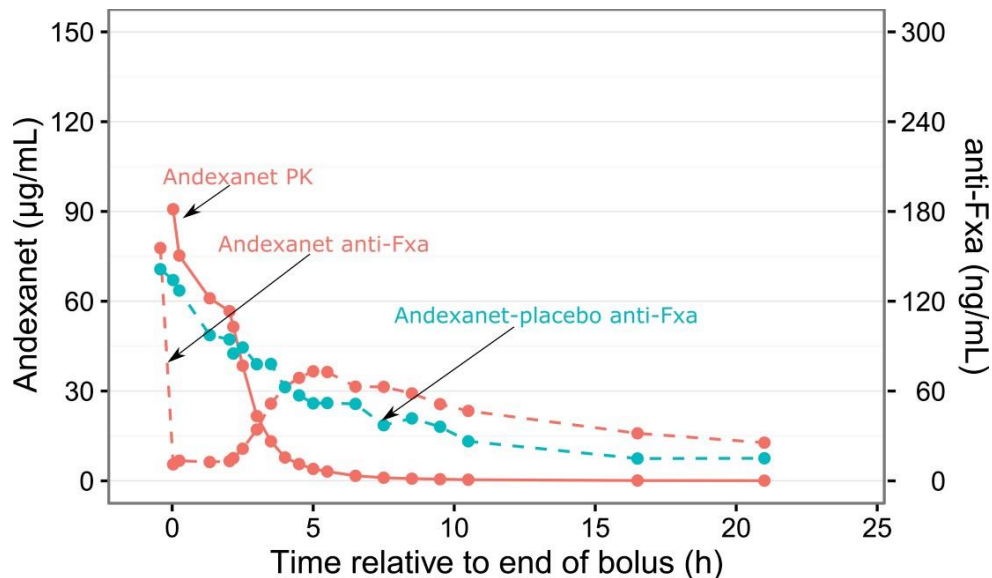
Based on the provided information, the rebound in anti-factor Xa activity can be explained by:

- i) Direct effect of andexanet resulting in an immediate reversal in anti-factor Xa levels



- ii) Sequestering anticoagulant from peripheral tissue as a consequence of administration of andexanet and the system reaching a new equilibrium;
- iii) Elimination kinetics of andexanet, which is reversibly bound to the anticoagulant;
- iv) Faster equilibration of protein binding kinetics as drug that has been mobilized into the system is both eliminated and reabsorbed into peripheral tissue reverting to natural disposition and elimination of apixaban.

These concepts are illustrated by briefly examining the time course of various moieties following administration of andexanet alfa (**Figure 6**).



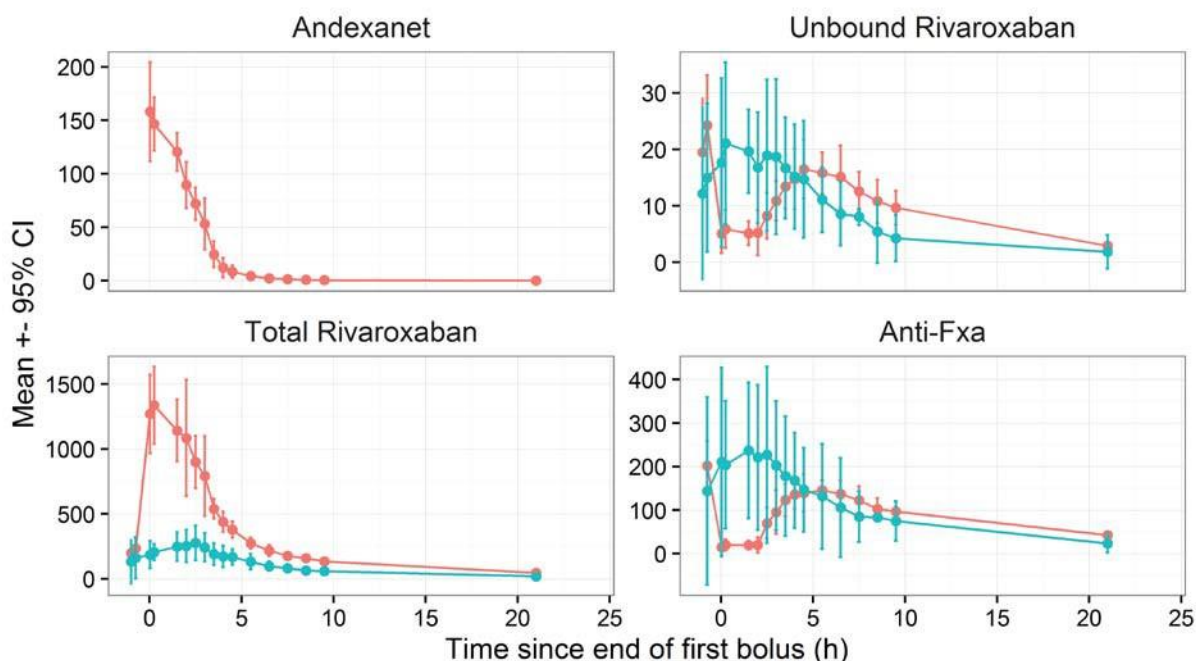
**Figure 6** Time course of plasma andexanet concentrations and anti-factor Xa levels following the administration of andexanet (Bolus: 420 mg; Infusion: 4 mg/min over 2 hours) or Placebo at steady-state C<sub>max</sub> following 5 days of administration of apixaban 5 mg BID. Note: The time course is truncated to 24 hours for ease of presentation. (Data source: study 12-502 [module 1] )

The reversal of factor Xa inhibitor effect can be attributed to a pharmacokinetic phenomenon as evidenced by an immediate decrease in unbound factor Xa inhibitor concentrations and a decrease in anti-factor Xa levels indicating immediate inactivation of the anticoagulant effect.

Corresponding to these changes there is an increase in the total factor Xa inhibitor concentration in plasma (bound + unbound) i.e., a significant increase in total-to-unbound ratio, indicating remobilization of drug from the peripheral tissues and immediate inactivation of the anticoagulant effect. These changes (decrease in anti-factor Xa and unbound factor Xa inhibitor; increase in total factor Xa inhibitor) are maintained throughout the duration of andexanet infusion. Elimination of andexanet is predominantly complete (b) (4) after the end of the infusion (half-life = (b) (4)). Correspondingly, there is a decrease in total-to-unbound ratio eventually reaching pre-andexanet alfa levels. However, given the reabsorption kinetics (i.e., central to peripheral), the total factor Xa inhibitor concentration is numerically higher compared to the placebo arm after stopping of the andexanet alfa infusion. The higher total factor Xa inhibitor concentrations also corresponds to relatively higher unbound factor Xa

inhibitor and in the absence of andexanet alfa results in a rebound of anticoagulant activity around 2-3 h after stopping andexanet alfa infusion. There is no suggestion that the observed increase in unbound factor Xa inhibitor concentration following the end of the andexanet infusion is due to alteration of coagulation pathways.

This phenomenon is illustrated for apixaban (**Figure 1**) and rivaroxaban (**Figure 7**) time-courses presented below.



**Figure 7** Time course of plasma andexanet alfa concentrations, unbound rivaroxaban concentrations, total rivaroxaban concentrations and anti-factor Xa levels following the administration of andexanet alfa (Bolus: 800 mg; Infusion: 8 mg/min over 2 hours - Red) or Placebo (Blue) at steady-state C<sub>max</sub> following 5 days of administration of rivaroxaban 20 mg QD. Note: The time course is truncated to 24 hours for ease of presentation. (Data source: study 12-502 [module 2] )

**d) The adequacy of the dosing regimen as it relates to:**

- i) The observed rebound in anti-fXa activity for subjects anticoagulated with apixaban and rivaroxaban. Given the higher than placebo levels of anti-FXa activity observed for rivaroxaban, please state whether additional premarket data are needed to evaluate this issue.
  - ii) The higher levels of anti-fXa activity observed in the confirmatory study, as compared to those achieved just prior to andexanet dosing in the healthy volunteer phase 3 trials.
- i. As stated above, the observed rebound in anti-factor Xa activity with the proposed 2-h infusion duration is of sufficient magnitude to inhibit coagulation to some degree. Additional pre-marketing data is not needed to understand the cause of the rebound. However, the solution to mitigate the rebound would require longer infusion

- durations. The modeling report (qsandexanet001.pdf) provided by the sponsor can be used to inform the necessary infusion duration based on time since last dose of the anticoagulant. The ongoing Phase 3b/4 study could also be modified to permit longer infusion durations based on the modeling analysis as safety information is collected in healthy volunteers.
- ii. In general, the exposures observed in the healthy volunteer studies are similar to those that have been observed in the registration trials for apixaban and rivaroxaban (see [Table 6](#)). We view the patient population in the Phase 3b/4 trial as representative of the registration trials and with the vast majority of the exposure range addressed in the healthy volunteer studies. In order to best address outlier patients such as those noted apixaban and rivaroxaban patients, a pragmatic approach would be to: i) administer andexanet alfa at as high a bolus/maintenance dose as safety data permits rather than attempting to tailor the dose to the individual anticoagulant or drug level; and ii) have a means of monitoring patients following administration to determine if the degree of reversal is sufficient. The first approach will mitigate a large fraction of outlier cases as the 800 mg bolus/8 mg/min infusion was sufficient in healthy volunteer studies where the anti-factor Xa levels were >300 ng/mL. The second approach will mitigate extensive outliers, such as the rivaroxaban patient noted as having baseline anti-factor Xa of 862.4 ng/mL. This patient also had a baseline rivaroxaban total drug concentration of 1060 ng/mL (note: values in 14-505 dataset for total drug are off by a factor of 100 as evidenced by all unbound drug concentrations are greater than all total drug concentrations). This concentration exceeds the 95<sup>th</sup> percentile from the registration Phase 3 trials for rivaroxaban (343 and 419 ng/mL for DVT and atrial fibrillation, respectively) and likely represents an extreme outlier. Such patients may be best addressed with monitoring and permissive language to utilize higher doses.

**e) Preliminary data from the confirmatory study show that a large percentage of subjects requiring urgent reversal have moderate renal impairment. The safety of andexanet in this population has not been evaluated; healthy volunteer studies excluded patients with renal impairment.**

- **i) Please comment on an acceptable approach to evaluate dosing in subjects with renal impairment.**
  - **ii) Please comment on the necessity to conduct a renal safety study. If such a study is necessary, please comment on the preferred PK/PD parameters to be incorporated and the appropriate population for the study.**
- i. From the provided information, it would be acceptable but not necessary, to evaluate andexanet alfa in healthy volunteers with renal impairment. Evaluating such healthy volunteers as part of the proof-of-concept studies could have ensured a better matching between patients in the proof-of-concept studies and the patient population that will be

administered anticoagulants. As is, the exposures observed in the healthy volunteer studies with apixaban and rivaroxaban are in agreement with the observed exposures of these drugs from the registration atrial fibrillation and deep vein thrombosis trials, as noted in (a).

- ii. A renal safety study is not needed to independently determine the safety of andexanet alfa in this population. There is sufficient information available from the healthy volunteer studies to support the mechanism of action of andexanet alfa and inform dosing. . The US package inserts for rivaroxaban and apixaban provide for dose adjustment based on renal function or factors contributing to estimation of renal (e.g., body weight, serum creatinine). This ensures reasonably similar exposure over the renal function range for rivaroxaban and apixaban. If renal function does play a critical role in andexanet alfa elimination, this would result in a prolonged half-life for andexanet alfa in patients with impaired renal function. This may be desirable, especially given the fact that the duration of infusion in general is not optimal (see response to 'b').

**f) Please comment on the appropriate role of thrombin generation levels to predict reversal of anticoagulant effect (bleeding) of rivaroxaban, apixaban and edoxaban anticoagulants.**

Thrombin generation is one of the collected pharmacodynamic markers that mirrors unbound drug concentration and anti-factor Xa activity following administration of placebo or andexanet (Figure 3). In the presence of an anti-factor Xa anticoagulant, a decrease in ETP can be observed that separates from normal baseline values. Over the dosing interval for apixaban and rivaroxaban, ETP levels return to the 5<sup>th</sup> percentile of baseline ETP values over approximately 12 hours. Consequently, when andexanet is administered, there is an immediate increase in ETP above the 95<sup>th</sup> percentile of baseline values. This degree of restoration was maintained throughout the duration of infusion. Post-infusion ETP levels are within the 5<sup>th</sup> to 95<sup>th</sup> percentile interval of observed baseline values while unbound factor Xa inhibitor, anti-factor Xa activity, and deviations from ACT baseline can still be detected. Because of this observation, ETP may not be ideal for determining if reversal of the anticoagulant effect has been achieved after completing the andexanet alfa infusion. However, ETP does appear to capture both andexanet alfa's on-target effect (i.e., occupying unbound factor Xa inhibitor) as well as its off-target effect of depleting free and total TFPI. It is this off-target effect on TFPI that may explain the increase over baseline ETP values during the infusion and elevated ETP levels after the end of the infusion despite the presence of unbound factor Xa inhibitor. As such, ETP may have value for assessing if excessive thrombin generation occurs, the duration it remains elevated, and when it returns to baseline.

**g) Given the dual mechanism of action of andexanet on TFPI and anti-fXa levels, the thrombin generation levels noted and the potential for a prothrombotic state, albeit with “supratherapeutic” anti-coagulant levels, in the target population, is it acceptable from a safety and efficacy standpoint to extrapolate the data from the low dose apixaban group of healthy volunteers (HV) in the absence of data in the HV group to support the high dose of andexanet in the apixaban group in order to recommend a “high dose” regimen for treatment of apixaban related bleeding.**

Yes, provided that the safety information for the high dose from other healthy volunteers (800 mg bolus with 8 mg/min over 2-hr infusion for rivaroxaban) is found to be acceptable. Based on the available information, andexanet alfa is capable of reversing the anti-coagulation effects across apixaban and rivaroxaban primarily mediated by binding to unbound factor Xa inhibitor in the systemic circulation. Different doses are needed to reverse the anti-coagulation effects based on the pharmacokinetics, protein binding, and volume of distribution for each of the drugs. Different infusion durations may also be needed as was discussed earlier in the review. While a lower bolus dose of andexanet alfa may be sufficient to restore normal hemostasis in patients administered apixaban, there is no data that suggests giving a higher than necessary dose poses any safety risks (i.e., giving 800 mg and 8 mg/min when a lower dose would suffice). In fact, this may be preferable as information regarding which anti-factor Xa anticoagulant a patient is on upon clinical presentation may not be available when treatment with andexanet alfa is initiated. In addition, there may be some patients, similar to the ongoing andexanet alfa Phase 3b/4 experience, with outlying apixaban concentrations relative to the apixaban registration trial experience. Such patients may require a higher dose of andexanet alfa to restore normal hemostasis. As such, the safety experience with using a high bolus dose (800 mg) could be leveraged to support the use of an 800 mg bolus dose and 8 mg/min maintenance dose in patients administered apixaban or other anti-factor Xa inhibitors.

## 4.SIGNATURES

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