

Mid-Cycle MEETING SUMMARY

Application type and number: BLA 125586/0
Product name: Coagulation Factor Xa (Recombinant), Inactivated [ANDEXXA]
Proposed indication: For patients treated with direct or indirect Factor Xa inhibitors when reversal of anticoagulation is needed when experiencing a major bleeding episode (b) (4)
(b) (4).
Applicant: Portola Pharmaceuticals Inc.
Meeting date & time: March 24, 2016, 4:00 pm – 6:00 pm, EST
Meeting Chair: Mikhail Ovanosov, PhD
Meeting Recorder: Thomas J. Maruna, MSc, MLS(ASCP), CPH

Background:

BLA 125586/0 was submitted as a rolling review. The initial modules received on November 6, 2015 included Nonclinical Module 2 (sections 2.4 and 2.6) and Module 4. The remaining modules, i.e., Module 1, Module 2, Module 3 and Module 5, were received on December 17, 2015, starting the review clock. The current action date for this BLA is August 17, 2016.

The product received breakthrough therapy designation on November 22, 2013 under IND 15089. The product also received Orphan designation for the proposed indication of “reversing the anticoagulant effect of direct or indirect Factor (F) Xa inhibitors in patients experiencing a serious uncontrolled bleeding event (b) (4) (b) (4) on February 23, 2015. A proprietary name review was conducted under IND 15089; the proprietary name, ANDEXXA, was found to be acceptable. The applicant has been asked to submit a request for proprietary name review under BLA 125586/0. This application is being reviewed under a priority review schedule and is subject to PDUFA V requirements.

FDA previously determined that the BLA for the reversal of anticoagulation with direct FXa inhibitors would be accepted for filing under an Accelerated Approval pathway. FDA may decide to ask the applicant to name the specific direct FXa inhibitors for which the product would be indicated in patients with severe major bleeding, if an Accelerated Approval pathway continues to be appropriate following the review of the data. At this time, there are insufficient data to support an Accelerated Approval pathway for the reversal of anticoagulation with indirect FXa inhibitors, including enoxaparin, due to limited or lack of sufficient evidence. In addition, there are insufficient data to support an indication for (b) (4) in patients receiving either direct or indirect FXa inhibitor anticoagulants.

ATTENDEES:

Discipline/Organization	Name	Deficiencies Identified
Regulatory Project Manager (RPM)	Thomas J. Maruna, MSc, MLS(ASCP), CPH	-
Chair	Mikhail Ovanesov, PhD	Yes
Office Director - OBRR	Jay Epstein, MD	-
Associate Director Regulatory Affairs	Alan Williams, PhD	-
Division Director - DHCR	Howard Chazin, MD, MBA	-
Deputy Division Director - DHRR	Mahmood Farshid, PhD	-
Chief, RPM Staff	Iliana Valencia, MS	-
Acting Chief, Laboratory of Hemostasis	Tim Lee, PhD	-
Chief, Clinical Review Branch	Bindu George, MD	-
Clinical Reviewer	Lisa Faulcon, MD	Yes
Clinical Team Lead	L. Ross Pierce, MD	-
Clinical Pharmacology Reviewer	Iftexhar Mahmood, PhD	-
Supervisory Toxicologist	Anne M. Pilaro, PhD	-
Pharmacology/Toxicology Reviewer	Yolanda Branch, PhD	Yes
CMC Reviewer	Yideng Liang, PhD	-
CMC Reviewer	Andrey Sarafanov, PhD	-
CMC Reviewer	Zuben Sauna, PhD	-
Deputy Director - OCBQ/DMPQ	Lori Norwood	-
OCBQ/DMPQ Team Lead	Deborah Trout	-
OCBQ/DMPQ Reviewer	Christine Harman, PhD	Yes
OCBQ/APLB Reviewer	Kristine Khuc	-
Chief, OCBQ/BIMO	Patricia Holobaugh	-
OCBQ/BIMO Reviewer	Haecin Chun	-
Chief, OCBQ/DBSQC	Lokesh Bhattacharyya, PhD	-
OCBQ/DBSQC Reviewer	Karen Campbell	-
OCBQ/DBSQC Reviewer	Tobin Grainne	-
OCBQ/DBSQC Reviewer	Mark Levi	-
OCBQ/DMPQ/Inspector	Joan Johnson	-
Statistical Team Lead	Renee Rees, PhD	-
Statistical Reviewer	Chunrong Cheng, PhD	-
Post-marketing Safety, Epidemiological/ Pharmacovigilance Reviewer	Faith Barash, MD	Yes
Consult Reviewer (CDER)	Rajnikanth Madabushi, MD	-

DISCUSSION: REGULATORY CONCLUSIONS / DEFICIENCIES

1. Review of Important Milestone Dates:

- a. Mid-Cycle Communication: April 4, 2016 (rescheduled post-meeting to April 8, 2016)
- b. Internal Late-Cycle Meeting: May 2, 2016
- c. External Late-Cycle Meeting: June 2, 2016
- d. Primary Discipline Reviews Due: May 13, 2016
- e. Secondary Discipline Reviews Due: May 17, 2016
- f. Advisory Committee: Ad Hoc – Late June – To be discussed internally
- g. Action Due Date (ADD): August 17, 2016
 - i. In the event of a Major Amendment (MA), the ADD would be November 16, 2016.

2. Reviewer Reports – Discipline Reviews

CMC/Product

Plan to complete primary review by May 13, 2016 pending the completion of the *Establishment Inspection Report* of (b) (4) (manufacturer of andexanet alfa Drug Substance), which is dependent on the timeliness of Portola's responses to our information requests (IRs) and 483 observations, if any.

Substantive issues with the greatest impact listed first:

1. The data on process development and validation are incomplete, including those on the validation of commercial Drug Product (b) (4) data on batch consistency, comparability of stability for (b) (4) batches, and in-process hold times. **Portola committed to submit additional data by Day 120, 16 April 2016.** In addition, validation of (b) (4) will be reviewed during the Pre-License Inspection (PLI) of (b) (4), scheduled for April 18 – 22, 2016.
2. The release specifications of (b) (4) Drug Product for excipients, identity, and impurities are deficient. Andexanet alfa is a mutated coagulation factor product manufactured at large scale, formulated at high concentration and administered at high doses. The inclusion of excipient specifications and enhanced identity tests ((b) (4) and characterization of (b) (4) (b) (4)) will provide assurance of consistent product quality to compensate for the limited manufacturing experience. **We will also send an IR for the validation reports of all currently used analytical methods.** Specifications will be established close to the goal date based upon results from all relevant studies and manufactured batches. We will request post-marking commitments (PMCs) for the full validation of all assays, and re-evaluation of specifications when additional manufacturing data are available.
3. Portola has not developed assays to detect anti-drug antibodies that may bind or neutralize endogenous Coagulation Factors X and Xa. Development of neutralizing antibodies against endogenous proteins is a potential serious adverse event, and FDA had requested Portola to develop these assays during the pre-IND meeting on 16 June 2009 (CRMTS #7089, Ref. PS000698). In the original IND submitted on 15 March

- 2012, Portola had included a commitment to develop these assays, but Portola now states that assays for neutralizing antibodies against FX and FXa activities are not needed because no antibodies that bind FX and FXa have been observed to date and because such inhibitory antibodies would be detected by the existing pharmacodynamics assays. Moreover, Portola does not plan to validate the pharmacodynamics assays for interference with neutralizing antibodies. **We will send Portola a repeated IR for the development of assays for inhibitory antibodies against Factors X and Xa**, and explain to Portola that additional data are needed to support the related claims in the *Prescribing Information, Risk Management Plan* (1.16.1 Risk Management), as well as to enable the assessment of unwanted immune responses during the on-going clinical trials (reference will be made to *FDA Guidance for Industry - Immunogenicity Assessment for Therapeutic Protein Products*).
4. The characterization of the thermodynamics and stoichiometry of the interactions between andexanet alfa and FXa inhibitors - (b) (4) rivoroxaban and apixaban - is deficient. We will request Portola to expand the existing (b) (4) (b) (4) study, which only used one andexanet batch and one inhibitor (b) (4). The expanded study will include a side-by-side comparison of the interactions between at least ^(b) representative batches each from (b) (4) ^(b) with all three inhibitors. The study report should be submitted as an amendment to the BLA 60 days before the action date, i.e., by 17 June 2016, and we would expect the results to be supportive of the comparability of the batches manufactured using the (b) (4); and the comparability of interactions between andexanet and the respective inhibitors.
 5. The characterization of (b) (4) is deficient. We will request Portola to explain the observed (b) (4) to protein which potentially has up to (b) (4) sites. If (b) (4) (b) (4) is confirmed, we will also request Portola to develop a release specification for (b) (4) content as a PMC.
 6. The comparability protocols for proposed manufacturing changes are deficient. We will request Portola to provide clear and specific information for the manufacturing changes that should include, but not be limited to, the rationale for the changes, knowledge and understanding of the process the changes are involved in, supporting information, comparability study design and protocol, test methods, justification and validation protocol for the quality attributes to be tested, test methods and acceptance criteria, and data analysis strategy including statistic assessment.
 7. The determination of potency and its specification which is expressed as “percent of a reference standard” is not suitable for the control of the unitage because there is no assurance of the stability (consistency) of the reference standard. We will request Portola to develop a potency unit for andexanet alfa that is traceable to the current (b) (4). The request will also include a PMC for the establishment of a potency specification using the new unit when sufficient manufacturing data are available.
 8. Portola did not provide sufficient stability data to support the proposed shelf-life of (b) (4) Drug Product manufactured using (b) (4). Although real-time stability data demonstrated no negative trends, the results from the accelerated

stability studies suggest product degradation. We will re-assess the proposed shelf-life when Portola submits additional stability data on Day 120, 16 April 2016 and Day 180, 15 June 2016.

9. We also identified several minor deficiencies in the validation studies of the manufacturing process and analytical methods, and will follow up during the upcoming PLI of (b) (4) scheduled for (b) (4).

The primary review will be tentatively complete, April 30, 2016 pending the completion of the Establishment Inspection Report of (b) (4) (andexanet alfa (b) (4) manufacturer) and the timely receipt of additional information in response to IRs that are sent.

The following substantial issue was identified during the review:

- Sensitivity and method validation of the Container Closure Integrity Testing (CCIT) is inadequate.
- Major deficiencies in the Comparability Protocol, NC-15-0681-P0001 Comparability of Andexanet Drug Product (b) (4) versus (b) (4) Scale-up

Other (non-substantive) issues that were identified

- Several OQ/PQ report summaries were not provided for critical equipment including the (b) (4) Lyophilizer, (b) (4) (b) (4) Vial Filling and Closing Machine, (b) (4) (b) (4)
- Need more details in regards to the use of (b) (4) (b) (4) (b) (4) in the manufacturing process
- Need more details if computer systems are used in critical manufacturing processes
- Need more details of the (b) (4) used for filling activities

Additionally, during the review, some areas have been identified as areas to be followed up on the upcoming PLI (Pre-License Inspection) of (b) (4) scheduled for (b) (4) (b) (4) thus additional issues may be identified depending on the outcome of the inspection.

Sensitivity and method validation of the Container Closure Integrity Testing (CCIT) is inadequate.

The CCIT information provided in the narrative of the submission was described only at a high level with few details in relation to the sensitivity of the (b) (4) method and the positive controls used in this method. The two positive controls described consisted of (b) (4) (b) (4) to simulate a container closure defect. The (b) (4) defect noted for the positive control is not adequate as this does not constitute a “critical” defect. . For the (b) (4) positive control, the firm did not include the actual report of the method validation (only providing a reference to this report in the BLA submission), thus no details in how this positive control translates to representing a positive control for “(b) (4)”. For CCIT, the positive controls and the sensitivity

of the assay are crucial in the interpretation of the results, and indicating whether the container is suitable in maintaining the integrity of the product. Without a scientifically sound study, the firm cannot demonstrate and ensure the integrity of the container, thus quality of the product (i.e. maintain the sterility)

The firm did provide the following report entitled M073-1 “Container Closure Validation Final Report” prepared by (b) (4), which is the facility indicated by Portola to perform the CCIT for the product. However, this report is written at a high level and does not specifically refer to or describe the (b) (4) studies described in Section 3.2.P.2.5 Microbiological Attributes of the BLA submission. The report M073-1 describes the testing of container closures (b) (4) with various (b) (4) that are then subjected to (b) (4). There are no details in regards to conversion of (b) (4) used to an (b) (4), thus no connection to the use of the (b) (4) tube noted for the positive control used in the (b) (4) (b) (4) studies. This report does not provide a sufficient amount of detail to make conclusions on the use and sensitivity of the positive controls used for the (b) (4) method described in Section 3.2.P.2.5 Microbiological Attributes of the BLA submission.

At this time, it appears that Portola will have to re-perform the CCIT testing, thus could have an impact on the timeline of this BLA.

Major deficiencies in the Comparability Protocol, NC-15-0681-P0001 Comparability of Andexanet Drug Product (b) (4) versus (b) (4) Scale-Up

Portola provided two Comparability Protocols in the BLA submission. These protocols are to cover changes to 1) (b) (4) process in which (b) (4) is manufactured in (b) (4) (CP NC-15-0663-P0001) and 2) (b) (4) manufactured from (b) (4) manufactured in (b) (4) (CP NC-15-0681-P0001). Recently, Portola requested a meeting in regards to CP NC-15-0681-P0001 for the DP portion of manufacturing to discuss the required number of PPQ lots needed to support the changes described in CP NC-15-0681-P0001. (b) (4) changes to the DP (b) (4) (process used to support BLA submission) were noted in CP NC-15-0681-P0001, which includes

(b) (4)

In reviewing the CP, major deficiencies were found in that the CP did not contain the typical information that is commonly expected in a CP, in particular, specific details in regards to the lyophilization process were not provided. Thus, the firm needs to amend this CP if we are to consider reviewing it as part of the approval of BLA. If the CP is not amended, the CP will have to be withdrawn from the BLA or approval will be impacted..

Plan for addressing issues and the reason for the suggested approach:

An information request should be sent to Portola to address the deficiencies in the CCIT. Depending on the response received from Portola in regards to the CCIT and if Portola will have

to re-perform the CCIT for the container closure, the first plan of action could be the use of a PMC with a strict timeframe to be completed. Additionally and depending on when data is received during the review cycle, a **major amendment** could be triggered extending the review clock.

CMC/In-Support Testing

Awaiting sterility test qualification report as mentioned in IR response dated January 29, 2016 and another outstanding IR submitted March 14, 2016. Primary discipline review expected to be completed by July 2016.

Recovery of (b) (4) in the presence of (b) (4) using (b) (4) ((b) (4) at (b) (4) was found to be (b) (4) which does not comply with (b) (4) requirements. The reviewer has requested requalification of (b) (4) in the presence of (b) (4) using (b) (4) at (b) (4)

Endotoxin qualification Drug Product (DP) was performed in (b) (4) but release testing is performed at (b) (4) Method qualification should be performed in the same facility where the testing is performed. Therefore, the reviewer has requested an endotoxin qualification report showing the DP is suitable for the intended method performed at (b) (4)

No lot release protocol is needed for this product as it is exempt.

A draft product testing plan has been created.

In-support testing of samples is currently being carried out for potency and we are waiting for the receipt of samples and reagents for the (b) (4) assay.

A completed testing plan is expected to be completed by early September. Approval of the testing plan will depend on whether or not there are labeling or naming issues on going that hold up finalizing the testing plan.

We expect that the in-support testing will be completed by the end of May/early June. The shipment of in-support samples, which were requested on 7 March 16, is supposed to occur 21 Mar 16.

The following analytical procedures appear to be sufficiently validated or are compendial methods which only require verification:

- Concentration by (b) (4)
- Purity by (b) (4)
- Purity by (b) (4)
- Visual Appearance
- pH
- (b) (4)
- Moisture Content

The applicant developed two (b) (4) assays to measure potency of the Andexanet Alfa drug product. (1) The Direct Potency assay measures the ability of Andexanet Alfa to bind to the direct FXa inhibitor (b) (4) and hence reverse the inhibition of FXa in a mixture of Adexanet Alfa, (b) (4) and FXa. (2) The Indirect Potency assay measures the ability of Andexanet Alfa to bind to the indirect inhibitor (b) (4) in a mixture of Andexanet Alfa, (b) (4) and FXa. Deficiencies in the validation results were concerned with a lack of information on the linearity measurement for both methods, as well as clarification on how the Reference Standard was qualified. It is expected that these issues will be addressed in the responses to the IRs described below.

An IR was submitted on February 26, 2016 for the Direct Potency Assay, which addressed how the Reference standard was qualified and requested further information for their linearity study, such as dose response curves and regression coefficients. An IR was submitted on February 26, 2016 for the Indirect Potency Assay, for clarification of samples used in the study as well as dose response curves and regression coefficients for the linearity study. Responses to the IRs have not yet been received.

Non-Clinical Pharmacology/Toxicology

The following pharmacology studies have not been reviewed to date: NC-12-0459, NC-12-0460, NC-12-0461, NC-12-0462, NC-13-0512, NC-13-0561, NC-13-0564, NC-13-0569, and NC-12-0662.

At this time, there is no information request. However, this is subject to change after further discussion with the clinical reviewer.

The final Pharmacology/Toxicology primary review memorandum for BLA 125586/0 will be completed, with supervisory concurrence, by May 5, 2016.

There are several significant issues identified during the review process:

- Based on product composition, the total amount of sucrose and mannitol in the high dose are substantial thereby raising significant concerns. This is of concern to patients with renal disease, diabetes mellitus and GI bleeds as high levels of mannitol and sucrose can exacerbate these problems.
- There is no clinical experience with repeat use of the product. Furthermore, repeat use of Andexanet is of concern because of potential adverse effects related to high sucrose and mannitol exposure (i.e. renal failure, etc.).
- The Applicant is seeking approval for use with all direct FXa inhibitors but there is limited preclinical and clinical data submitted for endoxaban. However, the Applicant is seeking approval for all direct FX inhibitors without supportive data.

To address some of the substantive issues identified the following recommendations should be made to the label:

- Add language to the label in the warnings and precaution section that is consistent with other products about high levels of sucrose and mannitol.
- A statement should be added to the label about repeat use of the product and that is not recommended.
- Include language about use in patients with diabetes mellitus, renal disease and GI bleeds and the potential concerns.

Clinical Pharmacology

Review of one clinical pharmacology study is not yet complete. Primary review is expected to be complete by the end of April, 2016.

Clinical

Unable to do a complete review of safety as the applicant refused to submit the requested CRFs for all subjects in the Phase 2 and Phase 3 studies, including those who prematurely discontinued andexanet, experienced infusion-related ARs and had ECG abnormalities.

March 10, 2016: ECG tracings requested and will be submitted as per Portola's response to IR

March 16, 2016: Response to request for CRFs and adjudication reports for ongoing confirmatory study pending. [Post-meeting note: In an amendment to the BLA, the applicant subsequently provided the requested CRFs, but indicated that adjudication reports for individual subjects in ANNEXA-4 are not available.]

Primary discipline review will be completed after April 11, 2016.

Clinical studies included in the BLA are:

- Safety and pharmacokinetic (PK) initial Phase 1 study (Study 11-501) of healthy subjects dosed with andexanet alone
- PK and pharmacodynamic (PD) Phase 1 study (Study 14-506) comparing elderly (≥ 65 years of age) and younger (18 to 45 years of age) healthy subjects dosed with andexanet in the presence of apixaban
- Dose-ranging Phase 2 study (Study 12-502) of healthy subjects dosed with andexanet in the presence of the various FXa inhibitors (apixaban, rivaroxaban, enoxaparin, and edoxaban)
- **Two Phase 3 trial of andexanet in the presence of either apixaban (14-503) or rivaroxaban (14-504) in healthy older subjects (50 to 75 years of age)**
- Data from 17 subjects enrolled in the confirmatory Phase 3b/4 study (14-505; multicenter, prospective, open-label study of andexanet in approximately 250 subjects presenting with acute major bleeding who have recently received apixaban, rivaroxaban, edoxaban, or enoxaparin).

Table 2.7.4-3: Subjects Treated with Andexanet in Phase 1, Phase 2 and Phase 3 Studies, by Factor Xa Inhibitor and Posology

Dose Regimens		fXa Inhibitor				Total/Dose
		Apixaban	Rivaroxaban	Edoxaban	Enoxaparin	
Bolus Only	90 mg	6				6
	210 mg	6	6		12	24
	400 mg ^a	24 + 20 ^b				44
	420 mg	6	6		6	18
	600 mg	6 ^d	6	6		18
	800 mg ^a		27	6		33
Bolus + Infusion	600 mg (420 mg + 4 mg/ minute for 45')	6				6
	880 mg (400 mg + 4 mg/min for 120') ^a	24				24
	900 mg (420 mg + 4 mg/min for 120')	6				6
	960 mg (720 mg + 4 mg/min for 60')		6			6
	1,280 mg (800 mg + 8 mg/min for 60')			6		6
	1,760 mg (800 mg + 8 mg/min for 120') ^a		6 + 26 ^c			32
Total subjects dosed						223

^a Doses in Phase 3 studies (14-503 and 14-504).

^b 24 subjects from Study 14-503 and 20 subjects from Study 14-506.

^c 26 subjects from Study 14-504 and 6 subjects from Study 12-502.

^d 420 mg bolus + 180 mg bolus from Study 12-502 Module 1.

Source: Summary of Clinical Safety (page 25/132)

Phase 3 Trials (Primary Safety/Efficacy Data)

Both phase 3 trials of andexanet were designed as randomized, double-blind, placebo-controlled trials to demonstrate the ability of andexanet to reverse anticoagulation of apixaban (Trial 14-503) or rivaroxaban (14-504) and evaluate safety of andexanet in older subjects (ages 50–75 years). Subjects were dosed to steady-state with apixaban or rivaroxaban, followed by an andexanet bolus that was started 3 (apixaban) or 4 (rivaroxaban) hours after the last dose (at the approximate steady-state maximum plasma concentration [C_{max}]).

The primary objective was to compare andexanet and placebo with respect to reversal of anticoagulation as measured by anti-FXa activity (surrogate marker), both after a bolus (Part 1 of each study) and after a bolus followed by a continuous infusion (Part 2). The primary endpoint was percent reduction in anti-fXa activity at the nadir, both after a bolus and after a bolus followed by a continuous infusion.

Secondary endpoints included:

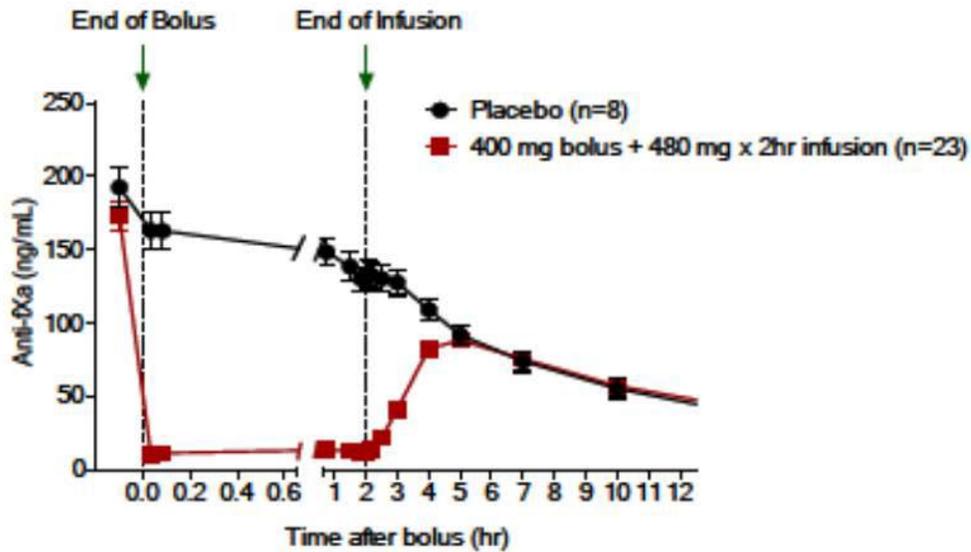
- The occurrence of $\geq 80\%$ reduction in anti-FXa activity from its baseline to nadir, when nadir was defined as the smaller value for anti-FXa activity at the +2 minute or +5 minute
- The change from baseline in free drug concentration (ng/mL) at nadir, when nadir was defined as the smaller value for free apixaban concentration at the +2 minute or +5 minute time point after the completion of the andexanet bolus.
- The change in thrombin generation and the occurrence of thrombin generation above the lower limit

Results

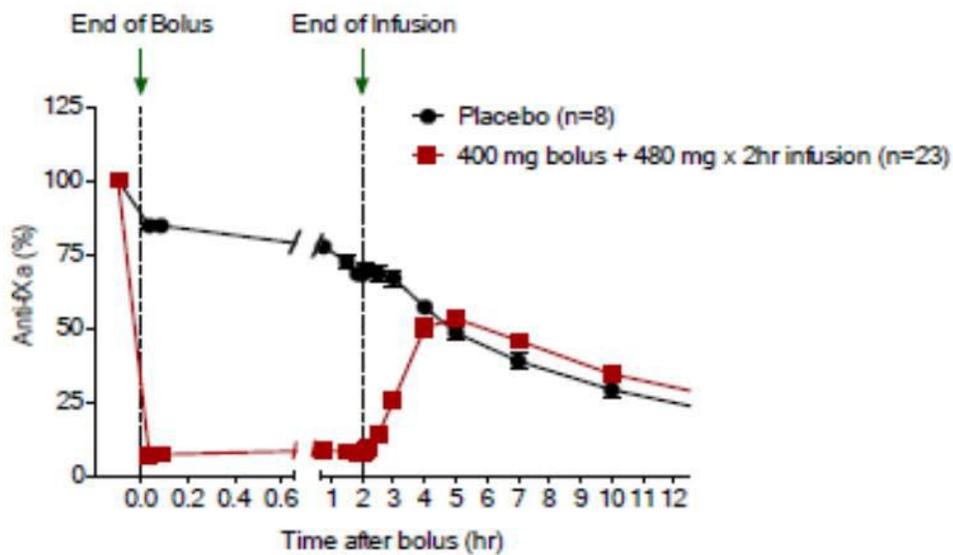
- a. 14-503 (Apixaban): 33/34 completed part 1 (24 andexanet; 9 control; 1 subject did not received andexanet); 31/32 completed part 2 (23 andexanet; 8 control; 1 subject's andexanet infusion was discontinued due to AE of mild hives and no follow-up anti-FXa levels were obtained)
 - i. 14-504 (Rivaroxaban): 41/41 completed part 1 (27 andexanet; 14 placebo); 37/39 completed part 2 (24 andexanet; 13 placebo; 2 in the andexanet group did not complete the study)
- b. Both studies won on all primary and secondary endpoints; significant differences ($p < 0.0001$) in the reduction anti-FXa activity was observed between subjects in the andexanet and placebo groups.
- c. Subject (b) (6) in the rivaroxaban study only had a reduction in anti-FXa activity of 39% (reduction of free rivaroxaban of 32%).
- d. In both studies, there was an apparent rebound of anti-FXa activity in the andexanet group. These findings were also noted in the phase 2 study for these anticoagulants (12-5-2, Modules 1 and 2), but were not noted for edoxaban (Module 4).

Figure 1: Time Course of anti-FXa Activity following andexanet bolus + infusion for healthy subjects anticoagulated with Apixaban (Phase 3 Study, Part 2)

(A). Anti-FXa (ng/mL)



(B). Anti-FXa (%)



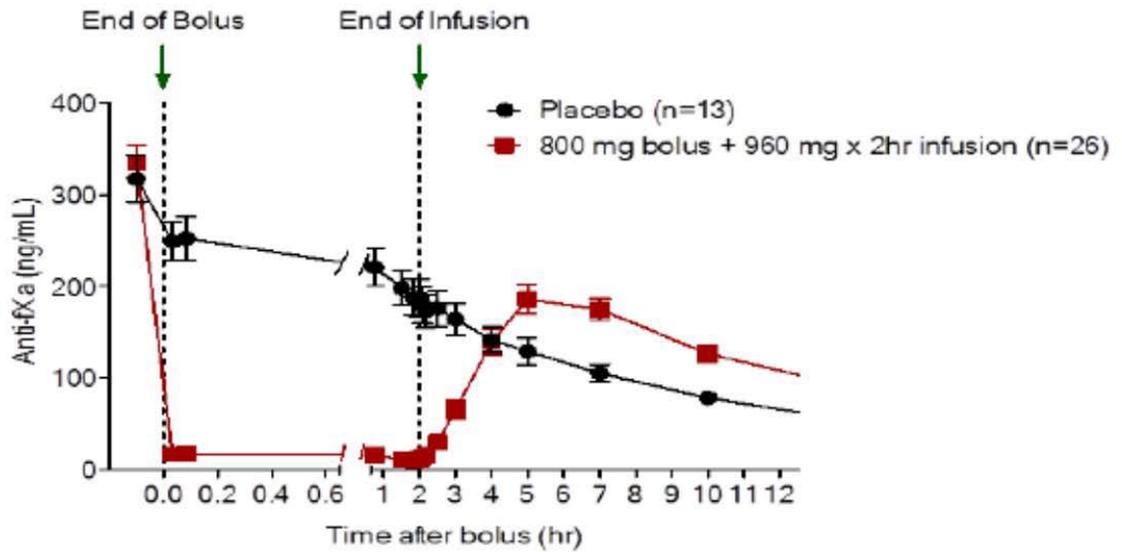
Note: Anti-FXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion. A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-FXa activity following andexanet treatment. The points on the graph represent the mean anti-FXa activity level and error bars illustrate standard error. Panel (A) shows Anti-FXa (ng/mL). Panel (B) shows Anti-FXa (%).

Source: [Listing 16.2.6.1b](#), [Table 14.2.2.1b](#)

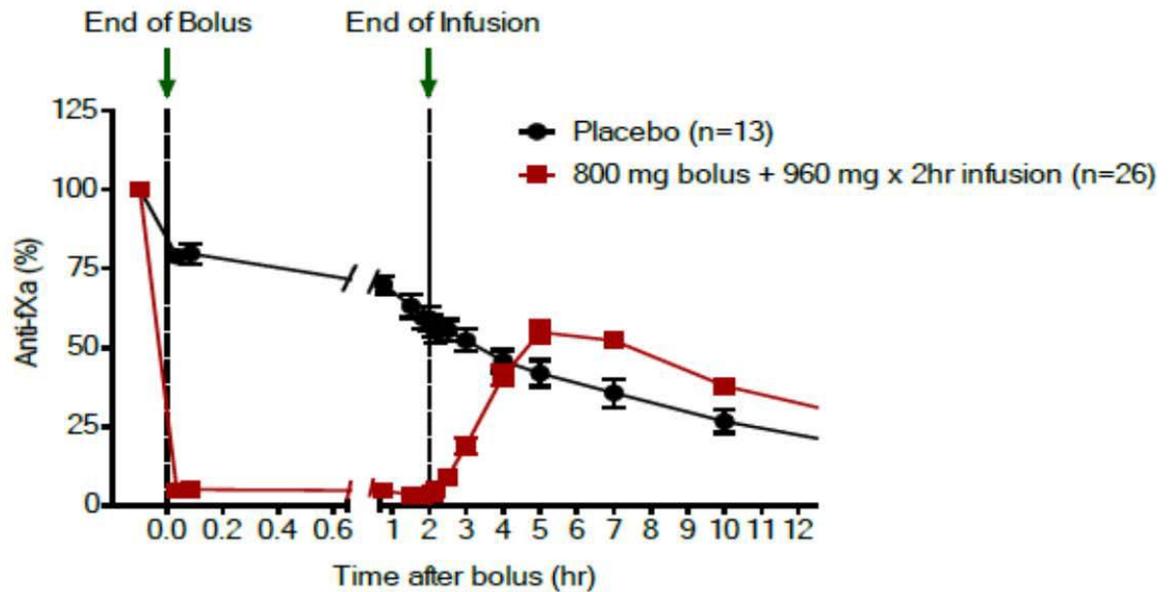
Source: CSR 14-503 page 70/141

Figure 2: Time Course of anti-FXa Activity following andexanet bolus + infusion for healthy subjects anticoagulated with Rivaroxaban (Phase 3 Study, Part 2)

(A). Anti-FXa (ng/mL)



(B). Anti-FXa (%)



Note: Anti-FXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion. A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-FXa activity following andexanet treatment. The points on the graph represent the mean anti-FXa activity level and error bars illustrate standard error. Panel (A) shows Anti-FXa (ng/mL). Panel (B) shows Anti-FXa (%).

FXa = Factor Xa, hr = hour; mITT = modified intent-to-treat.

Source: Listing 16.2.6.1b, Table 14.2.2.1b.

Source: CSR 14-504 page 72/138

Figure 2.5-5: Sustained Reduction of Rivaroxaban Free Fraction with Andexanet Infusion (12-502, Module 2)

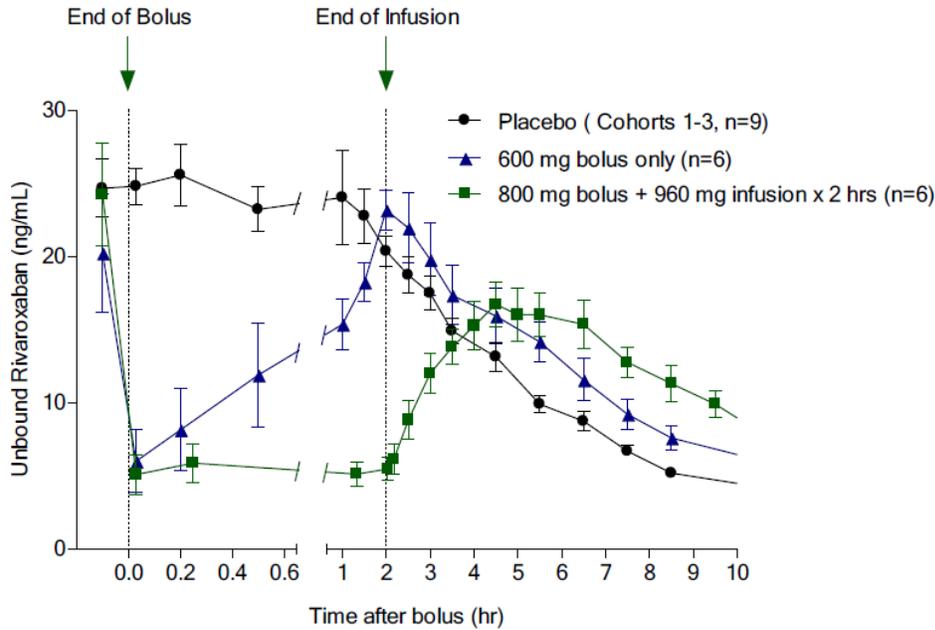
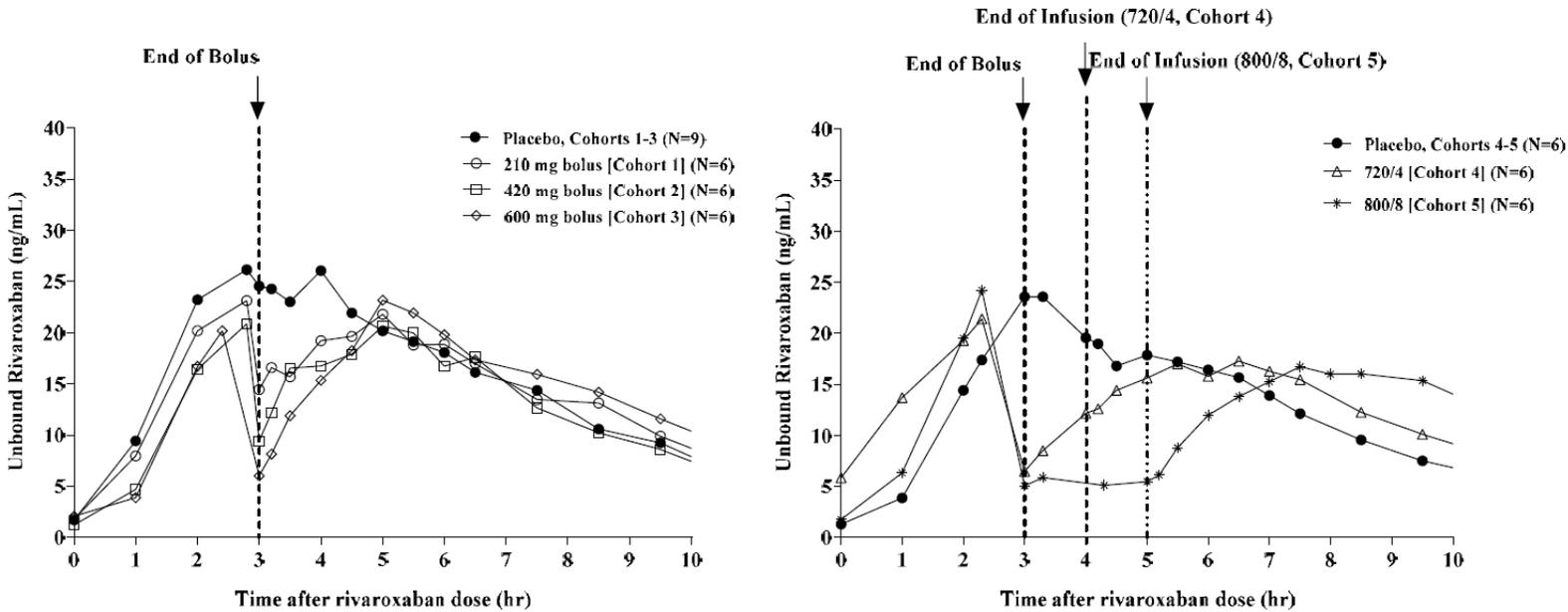
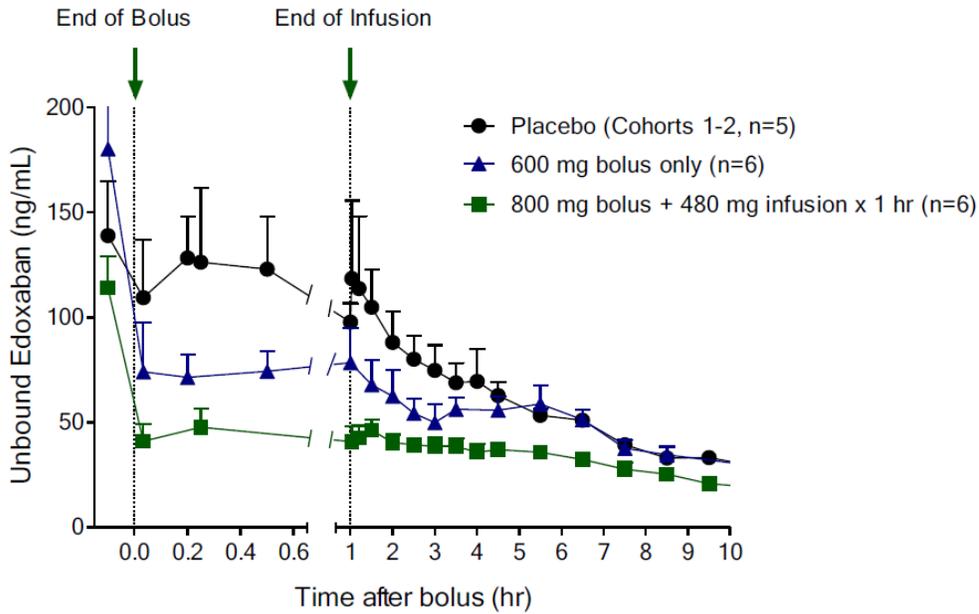


Figure 4: Unbound Rivaroxaban Concentrations on Day 6 after different Andexanet Dosing (Phase 2 Study, Module 2)



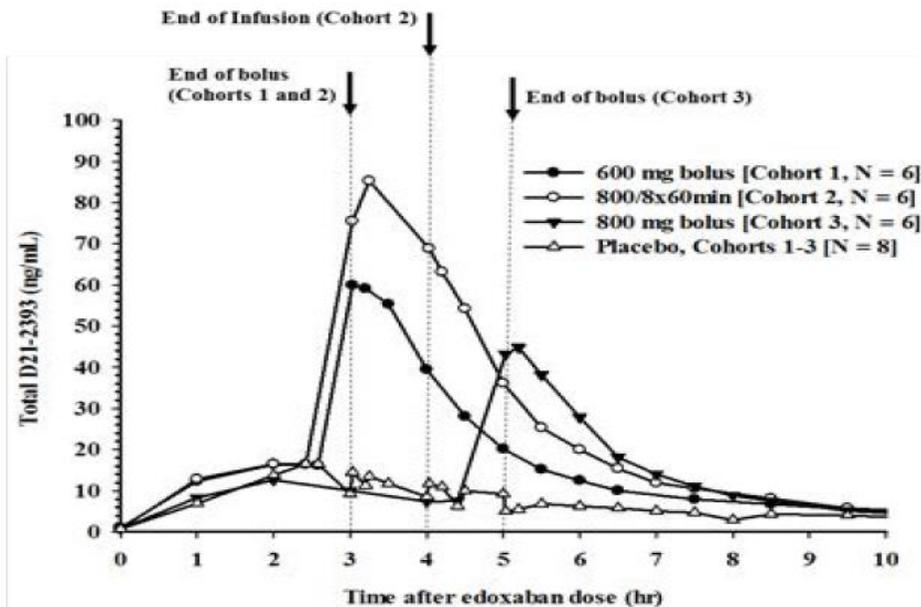
Source: 12-502 Module 2 Page 71.

Figure 5: Unbound Edoxaban Concentrations after different Andexanet Dosing (Phase 2 Study, Module 4)



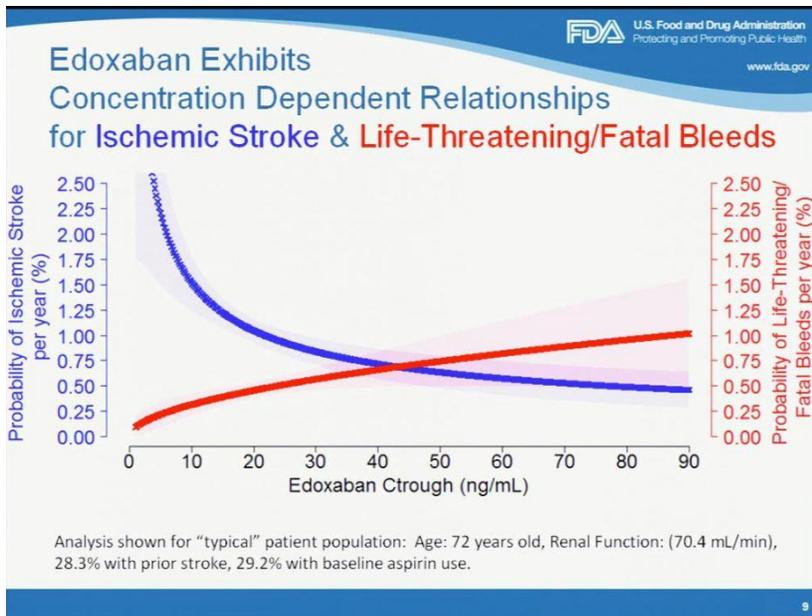
Source: 12-502 Module 4

Figure 6: Unbound Concentrations of Active Metabolite of Edoxaban after different Andexanet Dosing (Phase 2 Study, Module 4)



Source: 12-502 Module 4

Figure 7: Concentration Dependent Relationships for Ischemic Stroke and Clinically Significant Bleeding Events (Modeled Data)



Note: Edoxaban levels represent total levels

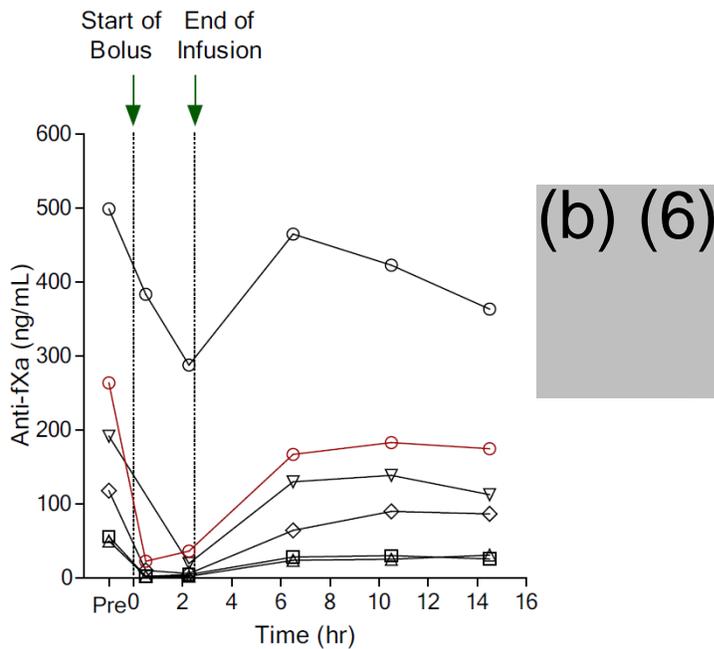
Confirmatory Study Phase 3b (14-505, ANNEXA-4; Supportive Safety/Efficacy Data)

Multicenter, prospective, open-label study of andexanet in approximately 250 subjects presenting with acute major bleeding who have recently received apixaban, rivaroxaban, edoxaban, or enoxaparin). The primary objectives are to demonstrate the decrease in anti-FXa activity following andexanet treatment and to evaluate the hemostatic efficacy of andexanet in patients who have acute major bleeding and reduced FXa activity. The primary efficacy endpoint is the achievement of hemostatic efficacy of stopping an ongoing major bleed at 24 hours from the start of the andexanet bolus, rated by the independent Efficacy Adjudication Committee as excellent or good. The relationship between percent decrease in anti-FXa activity and the achievement of hemostatic efficacy will be assessed as a secondary objective.

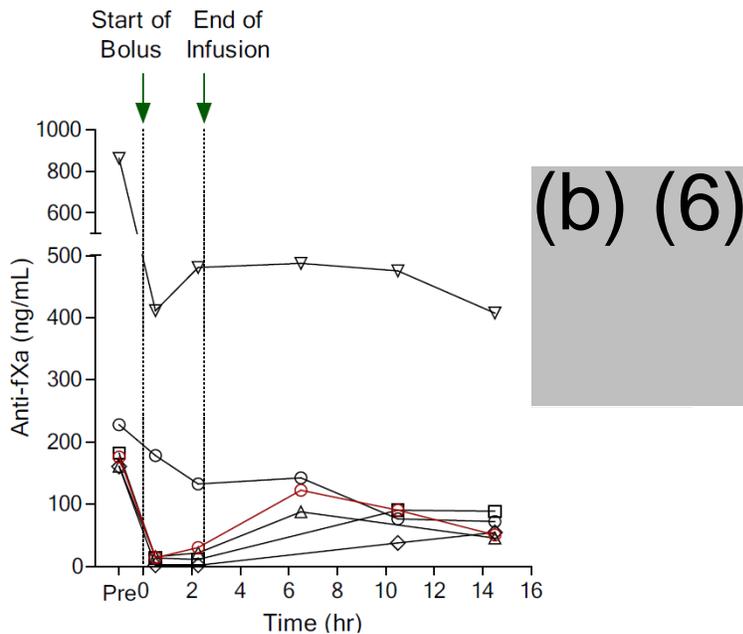
Results

1. Baseline anti-FXa levels were higher than those observed prior to andexanet administration in the phase 3 healthy volunteer trials in several instances, raising a question as to the appropriateness of extrapolating “efficacy” from the latter trial results to the target population. Confirmatory trial 14-505 also frequently had moderate renal insufficiency at baseline, which is known to slow the clearance of several FXa inhibitor anticoagulants.
2. Data from 17 subjects were submitted in the original submission; 14 subjects were adjudicated for post-treatment hemostatic efficacy outcomes, of which 12 were excellent (11) or good; 2 were poor and 1 was not evaluable.
3. The two subjects adjudicated to have poor hemostatic efficacy outcomes nevertheless exhibited substantial reductions in FXa inhibitory activity, raising a question as to the correlation between this surrogate marker and hemostatic efficacy. This will be explored further in the data on a larger number of subjects from this trial to be submitted in the safety update.

A. Patients with apixaban (N=6)



B. Patients with rivaroxaban (N=6)



Safety

A total of 264 subjects have been treated with andexanet, including 223 listed in the pooled safety analysis, 24 in the phase 1 study (11-501) and 17 in the confirmatory study.

The most common TEAE ($\geq 5\%$) in the pooled andexanet analysis that was greater than placebo was infusion-related reaction (17.5% vs. 6.4%, respectively). In both phase 3 studies, new post-baseline PR intervals >200 msec were noted in more than one subject, and an additional subject enrolled in the study of apixaban was noted to have a QTcF change from baseline >60 msec. ECG tracings for these subjects were not submitted in the BLA, but have been requested.

Anticipated Risks:

1. Thrombosis: no subjects in the healthy volunteers. Ten thrombotic events have been reported thus far in the ongoing confirmatory ANNEXA-4 trial.
2. Infusion-related reactions: 102 reports in 39 subjects in the andexanet group and 14 reports in 4 subjects in the placebo group; all mild except 7 reports of moderate in 3 subjects. All were related.
3. Potential for acute kidney injury, such as from the sucrose and mannitol content of the product, defined as increase in creatinine of ≥ 0.3 mg per dL (26.52 μmol per L) or ≥ 1.5 - to twofold from baseline. This risk is anticipated to be greater in patients with some degree of pre-existing renal impairment.

Based on product composition, we are expecting the following total doses of product and excipients:

- 18 vials, 100 mg each vial
- Volume: 180 mL
- Andexanet (factor Xa variant): 1800 mg
- Sucrose: 3.6 g
- Mannitol: (b) (4) g
- Polysorbate 80: 18 mg

Subject (b) (6) in study 14-504 (rivaroxaban) had an increase in creatinine of 0.3 noted at OPV day 43 (0.9 mg/dL pre-dose to 1.2 mg/dL); however, screening level was 1.0 and admission day-1 was 1.1.

4. Immunogenicity: 30/247 = 12.1% (overall); the initial frozen liquid formulation had a low rate of confirmed low titer non-neutralizing antibodies against andexanet (2/102; 2%); the rate observed for the lyophilized formulation was higher (28/146; 20%).

Unanticipated Risks:

1. Reports of Abnormal PR and QT values in Phase 3 Studies

14-503

In Part 1, PR intervals >200 msec was reported for 5 subjects in the andexanet group. In addition, 1 subject had a reported QTcF change from baseline >60 msec in the andexanet group; no subjects in the placebo group had reported abnormal PR interval or QTcF:

- Subject (b) (6) reportedly had a normal PR interval prior to andexanet administration (baseline inpatient Day 4 pre-dose value was 192 msec); however PR intervals >200 msec were noted at Discharge Day 8 (210 msec) and at the outpatient visit follow-up visit (OPV Day 43; 202 msec).
- Subject (b) (6) had PR intervals >200 msec at Baseline INPT Day 4 pre-dose (208 msec), INPT Day 4, 5 minutes post-bolus (204 msec), Discharge Day 8 (210 msec) and OPV Day 43 (210 msec).
- Subject (b) (6) had PR intervals >200 msec at Baseline INPT Day 4 predose (208 msec) and Discharge Day 8 (204 msec).
- Subject (b) (6) had PR intervals >200 msec at Baseline INPT Day 4 predose (208 msec), INPT Day 4, 5 minutes post-bolus (204 msec), Discharge Day 8 (206 msec) and OPV Day 43 (204 msec).
- Subject (b) (6) had PR intervals >200 msec at Baseline INPT Day 4 predose (214 msec), INPT Day 4, 5 minutes post-bolus (214 msec), Discharge Day 8 (224 msec) and OPV Day 43 (212 msec)
- Subject (b) (6) had QTcF change from baseline (412 msec) >60 msec at INPT Day 4, 5 minute post-bolus (488 msec). After review of the ECG tracings, the Sponsor concluded that the QT on the 5 minutes post-dose ECG was misread (machine reading: QT 438 msec, QTcF 488 msec), explaining “probably because the T-waves were very flat, so the end of the wave was somewhat hard to distinguish.” A repeat ECG was reportedly done 2 minutes later that read as a QT 374 msec and QTcF 406 msec by the ECG machine.

14-504

In Part 1, a newly abnormal PR interval >200 msec was reported for 1 subject in the andexanet group and 1 subject in the placebo group:

- Subject (b) (6) in the placebo group had a PR interval >200 msec at OPV Day 43 (202 msec); Baseline predose PR interval was 160 msec.
- Subject (b) (6) in the andexanet group had a PR interval on Day 43 of 208 msec. All earlier values were <200 msec. The baseline pre-dose PR interval was 192 msec.

In Part 2, PR intervals >200 msec was reported for 2 subjects in the andexanet group and no subjects in the placebo group:

- Subject (b) (6) had a PR intervals >200 msec at INPT Day 4 at 5 minutes post-bolus (202 msec); Baseline predose PR interval was 190 msec.
- Subject (b) (6) had a PR intervals >200 msec at INPT Day 4 at 5 minutes post-bolus (219 msec), INPT Day 4 at 5 minutes post-infusion (212 msec), Discharge Day 8 (217 msec) and OPV Day 43 (205 and 201 msec); Baseline predose PR interval was 197 msec.

Abnormal ECG Findings in Phase 1 and 2 Studies

11-501: Safety and pharmacokinetic (PK) initial Phase 1 study (Study) of healthy subjects dosed with andexanet alone

This was a single center, double-blind, randomized, placebo-controlled, ascending, single-dose study of andexanet or placebo, administered as a single IV bolus for 10 minutes in healthy

subjects. There were no subjects with QTcF intervals ≥ 450 msec that were not present predose. However, there were abnormal findings reported, including sinus arrhythmia, sinus bradycardia, borderline prolonged QTc, first degree atrioventricular block, left ventricular hypertrophy criteria, and incomplete bundle branch block), that occurred post-treatment (see attached line listing).

14-506: PK and PD Phase 1 study comparing elderly (≥ 65 years of age) and younger (18 to 45 years of age) healthy subjects dosed with andexanet in the presence of apixaban

This was a single center, prospective, open-label study of andexanet in healthy subjects who received apixaban 2.5 mg twice daily for seven doses followed by andexanet 400 mg IV. There were two parallel groups of ten subjects each: Group 1 was comprised of healthy subjects ages 18 to 45 and Group 2 was comprised of healthy subjects ages ≥ 65 . No subjects developed an increase in PR interval to > 200 msec or an increase in QTcF by >60 msec. However, the following abnormal findings were reported: QTcF change from baseline > 30 msec (Day 8, 2 subjects [20%]; Day 43, 5 subjects [25%]).

Study 12-502: Dose-ranging Phase 2 study of healthy subjects dosed with andexanet in the presence of the various FXa inhibitors (apixaban, rivaroxaban, enoxaparin, and edoxaban).

This was a single center, double-blind, randomized, placebo-controlled, study of andexanet or placebo, administered after subjects were dosed to steady-state with one of three direct FXa inhibitors: apixaban, rivaroxaban, edoxaban, or an indirect FXa inhibitor, enoxaparin.

Module 1 (Apixaban):

- Subject (b) (6) (Cohort 2, 420 mg) had a reported QRS interval > 120 msec at Day 7 (122 msec) and Day 48 (126 msec); baseline QRS interval was 118 msec.
- Subject (b) (6) (Cohort 3) had PR intervals of 202 msec and 204 msec, which were reported on Days 13 and 48.

Module 2 (Rivaroxaban):

- Subject (b) (6) (Cohort 1, 210 mg) had a baseline QTC of 421 msec with borderline prolonged QTC readings of 439 sec and 435 sec observed on Days 13 and 48, respectively
- Subject (b) (6) (Cohort 2, 420 mg), with a baseline QTcF of 418 msec, had a borderline prolonged QTC of 436 msec on Day 48.
- Baseline QRS interval for Subject (b) (6) (Cohort 2, 420 mg) was 118 msec. The QRS interval was > 120 msec at Day 7 (122 msec) and Day 48 (126 msec).

Module 3 (Edoxaban):

- Two subjects [Subject (b) (6) placebo; Subject (b) (6) 420 mg] had 1 or more PR intervals ≥ 200 msec.
- Short PR intervals were reported for 3 subjects.

Module 4 (Enoxaparin)

- Subject (b) (6) (600 mg bolus) had a reported short PR interval of 116 msec on Day 48.

Substantive Issues

1. Insufficient data to support (b) (4) indication (no data submitted; applicant aware).
2. Insufficient data to support reversal indication for enoxaparin (18 subjects received bolus only infusions, including 6/18 that received 420 mg (low) dose; none received high dose and none received bolus + infusion; applicant aware)
3. Limited data to support reversal indication for edoxaban (12 subjects received bolus only at the proposed dose; 6 received bolus + infusion at the proposed dose but infusion was only for an hour and not the proposed 2 hrs; reasonable to extrapolate).
 - a. The total edoxaban nadir levels post infusion are between 30-40 ng/ml. Based on the predictive model, the risk of fatal bleeding at the nadir levels remain a concern.
 - b. The % of unbound form of edoxaban > unbound apixaban and rivaroxaban. It may explain the less than optimal nadir levels achieved.
 - c. Thus, it may be necessary explore higher doses that result in deeper nadir levels before approval.
4. No data to support the proposed high dose for Apixaban (no subjects were dosed with 800 mg bolus or bolus+infusion)
5. No data to support the low dose for Rivaroxaban (no subjects were dosed at 400mg bolus +**4mg/minute infusion**. The nadir levels of unbound, total and anti-FX suggest incomplete reversal of the rivaroxaban effect.
6. The applicant has not provided adequate data to support their proposed target of lowering anti-FXa activity below 30 ng/mL to achieve hemostatic efficacy in patients with acute major bleeding.
7. The finding of higher baseline levels of FXa activity among several subjects in the ongoing confirmatory ANNEXA-4 trial than those observed in the phase 3 healthy volunteer studies may impact our extrapolation of efficacy from the healthy volunteer studies to the target population.
8. Adequate clinical data are lacking to identify the minimum duration that a reduction in anti-FXa activity needs to be maintained in order to achieve clinical hemostatic efficacy in patients with acute major bleeding. The observed rapid rebound in anti-FXa activity following the end of the infusion of andexanet in phase 3 trials of apixaban and rivaroxaban has also been observed in confirmatory trial patients and may have implications for continued elevated risk of bleeding.
9. Adequate dose finding in humans with respect to studying various durations of andexanet infusion have not been performed. The safety of infusions longer than 2 hours is unknown, which is problematic for a product that may have procoagulant activity.
10. Potential safety issue related to ECG changes (prolonged PR interval and QT)
11. Design of the confirmatory study is still being negotiated. Portola was advised to submit a protocol, revised SAP, and list of potential clinical trial sites for the prospective usual care study/arm by April 15th. FDA has advised the applicant that the current plan for statistical analysis of the primary hemostatic endpoint of the confirmatory trial, which involves comparison to a 50% minimum target for the percentage of subjects achieving excellent or

good adjudicated hemostatic efficacy ratings, is not acceptable and needs to be replaced with a superiority comparison to hemostatic efficacy achieved with unproven therapy in the requested prospective usual care cohort study.

Potential impact the substantive issues have on the review especially those which could prevent approval and impact the review timeline

1. No approval for (b) (4).
2. No approval for reversal for enoxaparin
3. Potential for no approval for Edoxaban; Due to the differences in the activity of Andexanet and Pharmacokinetic properties of Edoxaban we have limitations in our ability to extrapolate from apixaban and rivaroxaban data
 - a) Absolute levels of unbound edoxaban nadirs are higher than with Apixaban and continue to pose a fatal bleeding risk based on the predictive model.
 - b) Proportion of unbound edoxaban is higher than that for unbound apixaban
 - c) This also raises the issue that a class approval maybe problematic and may also impact the design of the confirmatory study with the need for a stratification design.
4. Potential to not approve the low dose regimen for Rivaroxaban. The data from the Phase 2 study for low dose limited to comparable (420mg) bolus dose only. The applicant is requesting approval for both high (800 mg bolus + 8mg/min infusion for 2 hrs) and low doses (400mg bolus + 4 mg/min).
 - a. 0 subjects received the low dose infusion with the 420mg bolus
 - b. For the 6 healthy subjects who received 420mg bolus dose the nadir unbound Rivaroxaban levels at the end of bolus was approximately 2 times the nadir for the 800mg bolus dose. Since the nadir levels are dependent on the bolus dose and absent correlation with the nadir levels with hemostasis, we are uncertain that the nadirs are adequate to result in hemostasis.
 - c. For 6 subjects who received 720mg bolus + **4 mg infusion** dose the unbound rivaroxaban levels continued to rise during the 2 hr infusional period. Thus we are uncertain that the low dose 4 mg infusional is adequate to maintain nadir levels during the 2 hr infusional period.
5. No approval for high dose apixaban; however, there is sufficient data to support dosing for the low dose.
6. Input from SGEs and BPAC will be sought with respect to whether lack of identification of a target threshold for reducing anti-FXa activity and for identifying the minimum duration of reduction in anti-FXa activity to achieve clinical hemostasis may impact our ability to rely on the surrogate marker for providing substantial evidence of effectiveness.
7. Data from the larger number of ongoing ANNEXA-4 confirmatory trial subjects to be submitted with the safety update will be examined as to whether these data may undermine our earlier opinion that changes in anti-FXa activity would be reasonably likely to predict clinical benefit in patients with acute major bleeding. Such a finding may impact the appropriateness of using the accelerated approval mechanism for this application.
8. Awaiting input from (b) (4) with regard to ECG findings, but findings could result in PMR/REMS (preliminary input is this is unlikely to be a safety issue) and may warrant additional safety monitoring in the confirmatory study.

9. If the protocol is not received by April 15th, we may issue a CR. If it is received by the 15th and significant revisions/negotiations are warranted we may consider the submission as a major amendment.

Plan for addressing issues and the reason for the suggested approach

1. No approval for (b) (4). The applicant has been advised that they can submit a supplemental BLA once (b) (4) data is obtained; a (b) (4) protocol has not been reviewed by FDA.
2. No approval for reversal for enoxaparin. The applicant has been advised they can submit a supplemental BLA once they obtain adequate data to support safety and efficacy for enoxaparin.
3. Extrapolate from the higher infusion rate to allow approval for edoxaban. Request revisions to the confirmatory study to ensure that sufficient data for edoxaban is obtained in the confirmatory study.
4. Awaiting input from (b) (4) but revisions to the safety monitoring for future studies is likely.
5. The confirmatory study will be a Title IX PMR. We agreed to review a study synopsis for the prospective usual care cohort study which is to serve as a control for ANNEXA-4 and provide feedback. At the time of approval, an agreed upon protocol and projected milestones are all that is required to document due diligence on the part of the applicant in getting the confirmatory study done. This will require revision of the statistical analysis plan for ANNEXA-4 as well as agreement on the protocol and analysis plan for the prospective usual care cohort study.

Outstanding Regulatory Questions

- The review team would like to understand that if the team is unable to demonstrate of correlation of Anti-Xa with bleeding risk/hemostasis, would that result in not approving the product under AA with a decision to defer approval until such correlation can be demonstrated or until the results of the confirmatory study (clinical benefit endpoints) are available. Alternatively, will the decision to grant approval move forward (assuming no major unresolvable review issues) given our understanding as described in the 2nd bullet below.

Background

- Prior to the November 14, 2015 meeting with Portola the review team had considered accepting the BLA under the AA path, with the proviso to evaluate the correlation between Anti-Xa levels with bleeding risk or achieving hemostasis to support use of Anti-Xa as a surrogate. The clinical data to evaluate the bleeding risk was to be obtained through the available data for subjects in the ongoing confirmatory study in bleeding subjects.
- Following the decision on November 14, 2015 to accept the BLA under AA based on the understanding (based on the regulations rather than the Guidance and CDER/OHOP's feedback on their approach to how a surrogate endpoint is considered) that plausible

mechanism of action was sufficient to allow us to consider anti-FXa levels as a surrogate. [It was also assumed at that time that interim data from the confirmatory study that would be available during the original BLA review cycle would involve too few subjects to permit an evaluation of the correlation or lack of correlation between anti-FXa levels and hemostatic efficacy.]

Epidemiology

The pharmacovigilance Plan has been reviewed. There are no post-marketing data to review. The sponsor has agreed to submit a protocol for a confirmatory study, which will be reviewed when it arrives (expected April 15). Any study that will continue into post-marketing will be reviewed, and could possibly change our assessment. Additionally, should the submitted protocol contain a pharmacovigilance plan, this will be reviewed after receipt.

Primary review is expected to be completed by April 18, 2016 after receipt of protocol and additional data to be submitted on April 15, 2016.

Should the submitted protocol include plans to collect data into the post-marketing period, this could change how we assess the pharmacovigilance plan.

If the protocol to be submitted includes a separate pharmacovigilance plan, that will be reviewed as a separate document. Adverse events and potential safety issues will be reviewed from the totality of data.

There do not appear to be any substantive safety issues at this time.

Statistical

All statistical related areas are completely reviewed. Primary review is expected to be completed by May 13, 2016.

There are no substantial issues.

The following findings apply to studies 14-503 and 14-504:

1. These two studies won all the primary and secondary efficacy endpoints: significant difference of anti-fXa activity reduction was observed between subjects in the ANDEXXA and placebo groups, similarly for the free apixaban/rivaroxaban concentration, and restoration of thrombin generation. For example, for Study 14-503, in Part 1, the mean percent change of anti-fXa activity from baseline to the nadir was -93.86% ($\pm 1.650\%$) for the ANDEXXA group and -20.71% ($\pm 8.559\%$) for the placebo group ($p < 0.0001$).
2. The results can be verified. The applicant will be requested to correct a few minor errors in tables of results presentation.
3. In both studies, there was an apparent rebound of the anti-fXa activity in the ANDEXXA group. The curves from the two groups (ANDEXXA and placebo) became very close

around 2 and 4 hours after bolus, for Part 1 and Part 2 respectively. This short duration of reversal could be concerning. I will defer to the clinical team for evaluation.

The following finding applies to Study 14-504:

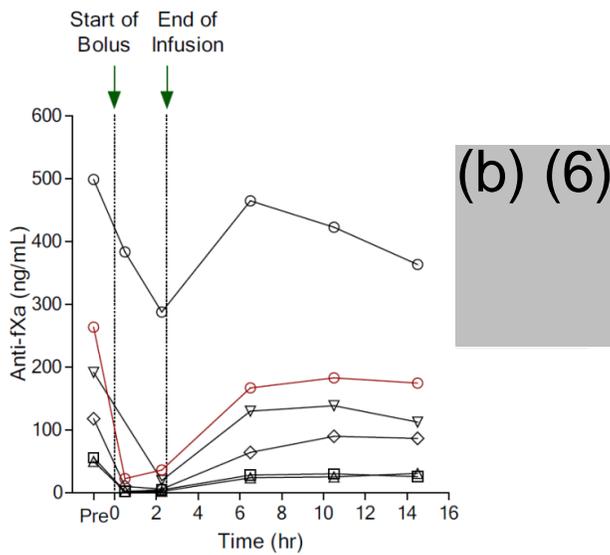
1. In Part 1 of Study 14-504, one subject ((b) (6)) from the ANDEXXA group seemed to be an “outlier” on efficacy endpoints. The applicant may need to provide an explanation on this subject.

The following finding applies to Study 14-505 (Phase 3b):

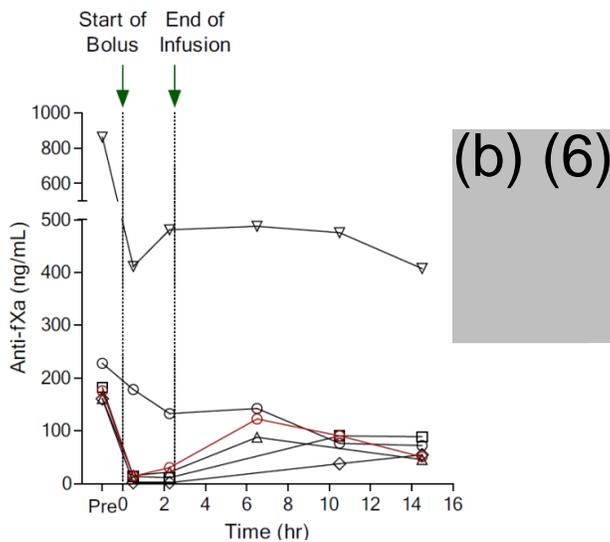
2. The primary efficacy endpoint is the achievement of hemostatic efficacy of stopping an ongoing major bleed at 24 hours from the start of the ANDEXXA bolus, rated by the independent Efficacy Adjudication Committee (EAC) as excellent or good.

At the time of submission, 14 subjects were adjudicated for post-treatment hemostatic efficacy outcomes. Among them, 12 were either excellent (11) or good (1), 2 were poor, and 1 was not evaluable. The two subjects with poor hemostatic efficacy outcome (ID (b) (6) and ID (b) (6)) had consistent reductions in anti-fXa activity with other subjects (see the figure below). Based on the limited available data, an obvious correlation between anti-fXa activity and hemostatic outcome is not observed.

A. Patients with apixaban (N=6)



B. Patients with rivaroxaban (N=6)



An IR is planned to be sent.

BIMO

BIMO inspection assignment memos for Site 001 (Protocol 14-503) and Site 002 (Protocol 14-504) are pending completion. CBER requested ORA to complete the BIMO inspections for this BLA by March 31, 2016. EIRs for both inspections will be reviewed upon receipt.

BIMO will complete the final discipline review after all Establishment Inspection Reports (EIRs) are received and reviewed.

The following table summarizes BIMO inspections that will be conducted:

Site ID	Study Site	Location	Protocol	Status
001	Celerion	Tempe, AZ	14-503	Inspection not completed EIR pending receipt
002	West Coast Clinical Trials, Inc.	Cypress, CA	14-504	Inspection not completed EIR pending receipt

No substantive review issues/major deficiencies have been identified, at this time.

Labeling

On February 1, 2016, Portola Pharmaceuticals (Portola) submitted a PNR request for its proposed factor Xa (fXa) anti-coagulation reversal agent. The proposed proprietary name is **ANDEXXA**. There is no alternative proprietary name proposed.

According to the sponsor, the name **ANDEXXA** (pronounced *an dex' ah*) is derived from its proper name, andexanet alfa, a recombinant modified human factor Xa (fXa) anti-coagulation reversal agent. The proposed indication is for urgent reversal of anticoagulation with a direct or indirect fXa inhibitor in situations such as

- life-threatening or uncontrolled bleeding.
- (b) (4) .

ANDEXXA will be available as a reconstitutable powder for intravenous injection. It will be supplied as 100mg of a reconstitutable andexanet alfa powder per vial. The product will be stored in a refrigerator (2 - 8°C; 36 - 46°F). It is intended to be administered in hospital and inpatient emergency rooms as a one-time intravenous bolus or infusion, depending on the situation.

The sponsor provided a proprietary name review conducted in October 2015 by the Drug Safety Institute, who found **ANDEXXA** an acceptable proprietary name candidate.

The proposed proprietary name, **ANDEXXA**, was screened against the following:

- Obvious similarities in spelling and pronunciation
- Manufacturing characteristics
- Medical and/or coined abbreviations
- Inert or inactive ingredients
- Combination of active ingredients
- United States Adopted Name (USAN) stems
- Same proprietary name for products containing different active ingredients
- Reuse of proprietary names
- Dosage form or route of administration
- Dosing interval

- Established or proper name
- Modifiers as components of a proprietary name
 - Use of numerals as modifiers
 - Device-related modifiers
 - Descriptive modifiers
- Brand name extensions (Umbrella branding)
- Dual proprietary names
- Foreign drug proprietary name
- Prescription-to-OTC switch
- Use of symbols
- Incorporation of the sponsor's name

The proposed proprietary name, **ANDEXXA**, is not regarded to be false, misleading or fanciful.

Since drug products are prescribed through written, verbal, and/or electronic orders, such forms of communication may lead to medication errors, particularly if proprietary or established names sound or look alike. APLB conducted a search using POCA, with DPRF, Drugs@FDA, Cerner US Legend and OTC, CBER Biologic, Orange Book, and RxNorm as data sources, to identify names of concern with potential combined orthographic and phonetic similarity to **ANDEXXA**.

The combined orthographic and phonetic matches are listed below:

Proposed name: ANDEXXA Strength: 100 milligrams of andexanet alfa Dosage Form: powder for reconstitution Storage temperature: 2 - 8°C or 36 - 46°F			
<u>Name of Concern</u>	<u>Combined Match Percentage Score</u>	<u>Dosage Form and Strength</u>	<u>Notes</u>
EUFLEXXA	66	Injectable prefilled syringe	1% sodium hyaluronate
ASMANEX	60	Aerosol Inhaler	mometasone furoate
ANEXSIA	57	Oral tablet	hydrocodone/acetaminophen

Although these names are moderately similar, differences in dosage form, dose, and strength decrease the risk of confusion.

The Advertising and Promotional Labeling Branch (APLB) has completed the review of the proposed proprietary name, **ANDEXXA**, a recombinant modified human factor X (fXa) protein.

The proposed proprietary name, **ANDEXXA**, has been found acceptable.

3. Advisory Committee Meeting

STN 125586/0 Mid-Cycle Meeting dated: March 24, 2016

An ad hoc advisory committee meeting has been scheduled for June 20 & 21, 2016.

4. National Drug Code (NDC) Assignments/Product Packaging

NDC codes are still under review. The RPM will complete primary review by June, 2016.

5. Proper Naming Convention

Coagulation Factor Xa (Recombinant), Inactivated

6. Information to be included in the Mid-Cycle Communication

Agenda is pending and will be sent to the applicant by April 7, 2016

7. Issues to be presented to Center Management

Acceptance of the surrogate marker to support continued review under an accelerated approval pathway.