

Summary Basis for Regulatory Action

Date: May 3, 2018

From: Mikhail Ovanesov, PhD, Chair of the Review Committee

STN#: BL 125586/0

Applicant Name: Portola Pharmaceuticals Inc.

Date of Submission: August 3, 2017

Goal Date: May 4, 2018

Proprietary Name/ Established Name: ANDEXXA / coagulation factor Xa (recombinant), inactivated-zhzo

Indication: For patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under Accelerated Approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban and rivaroxaban.

Recommended Action:

Certain members of the Review Committee recommend approval of this biologics license application (BLA) based on the data relevant to their areas of expertise. However, the clinical reviewer and supervisor conclude that the safety and efficacy data for ANDEXXA are not adequate to support approval, and therefore, do not recommend approval of the BLA. The Director of the Office of Tissues and Advanced Therapies (OTAT) concludes that the BLA provides substantial evidence of effectiveness and that ANDEXXA has a favorable benefit-risk profile sufficient to support Accelerated Approval of ANDEXXA for the proposed indication.

Review Office Signatory Authority:

Wilson W. Bryan, MD, Director, Office of Tissues and Advanced Therapies

- I concur with the summary review.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

Office of Compliance and Biologics Quality Signatory Authority:

Mary A. Malarkey, Director, Office of Compliance and Biologics Quality

- I concur with the summary review for the responsibilities assigned to the Office of Compliance and Biologics Quality.**
- I concur with the summary review and include a separate review to add further analysis.**
- I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	Reviewer name, Document date
CMC Reviews <ul style="list-style-type: none"> • <i>CMC (product office)</i> • <i>Facilities review (OCBQ/DMPQ)</i> • <i>Establishment Inspection Report (OCBQ/DMPQ)</i> 	Mikhail V. Ovanesov, PhD: August 17, 2016 April 26, 2018 Wojciech Jankowski, PhD: August 15, 2016 April 18, 2018 Ze Peng, PhD: August 4, 2016 Yideng Liang, PhD: August 15, 2016 May 1, 2018 Andrey G. Sarafanov, PhD: August 16, 2016, April 20, 2018 Christine Harman, PhD: August 12, 2016 January 4, 2018 Joan Johnson August 17, 2016 Joan Johnson, Donald Ertel, Yideng Liang, PhD, and Mikhail V. Ovanesov, PhD: September 19, 2016
Clinical Reviews <ul style="list-style-type: none"> • <i>Clinical (product office)</i> • <i>Postmarketing safety epidemiological review (OBE/DE)</i> • <i>BIMO</i> 	Lisa Faulcon, MD and Bindu George, MD: August 12, 2016 Howard Chazin: August 16, 2016 Bindu George, MD: April 22, 2018 Tejashri Purohit-Sheth, MD: April 27, 2018 Wilson W. Bryan, MD: May 2, 2018 Faith Barash, MD, MPH: August 12, 2016 April 13, 2018 Haecin Chun, Erin McDowell, and Dennis Cato: June 23, 2016 January 18, 2018
Statistical Review(s) <ul style="list-style-type: none"> • <i>Clinical data</i> 	Chunrong Cheng and Renee Rees: July 26, 2016 April 16, 2018
Pharmacology/Toxicology Review <ul style="list-style-type: none"> • <i>Toxicology (product office)</i> • <i>Animal pharmacology</i> 	Yolanda K. Branch, PhD, and Anne M. Pilaro, PhD: August 3, 2016
Clinical Pharmacology Review	Iftekhar Mahmood, PhD: August 17, 2016
Labeling Reviews <ul style="list-style-type: none"> • <i>APLB (OCBQ/APLB)</i> 	Kristine Khuc, PharmD: August 5, 2016 April 4, 2018 January 12, 2018

Document title	Reviewer name, Document date
Additional reviews not captured in above categories <ul style="list-style-type: none"> • <i>QC, Test Methods, Product Quality (OCBQ/DBSQC/LACBRP)</i> • <i>Lot Release Protocol/Testing Plan (OCBQ/DBSQC/QAB)</i> • <i>QC, Sterility and Endotoxin (OCBQ/DBSQC/LMIVTS)</i> • <i>Proprietary Name Review (OCBQ/DCM/APLB)</i> • <i>Immunogenicity Assessment (product office)</i> 	Grainne Tobin, PhD: August 16, 2016 February 5, 2018 April 25, 2018 Hsiaoling Wang, PhD: August 12, 2016 March 6, 2018 Mark Levi, PhD: June 20, 2016 Varsha Garnepudi, MS: May 1, 2018 Simleen Kaur: June 23, 2016 Oluchi Elekwachi, PharmD, MPH: February 16, 2016 Kristine Khuc, PharmD: April 4, 2018 Zuben Sauna, PhD: August 15, 2016
Consult reviews <ul style="list-style-type: none"> • <i>Clinical (CDER/OHOP/DHP)</i> • <i>Clinical Pharmacology Review (CDER/DCP I)</i> • <i>Extractables/Leachables, Toxicological Assessment (product office)</i> 	Lori A. Ehrlich, MD, PhD, R. Angelo de Claro, MD, and Ann T. Farrell, MD: June 23, 2016 Lars Johannesen, PhD, Jeffry Florian, PhD, Rajnikanth Madabushi, PhD, and Mehul Mehta, PhD: July 15, 2016 Jennifer Reed, PhD April 02, 2018
Regulatory Project Manager (product office)	Thomas Maruna and Jean Gildner
Advisory Committee summary	Not presented to an advisory committee

1. INTRODUCTION

STN BL 125586/o is an original biologics license application (BLA) submitted by Portola Pharmaceuticals Inc. (Portola) for *coagulation factor Xa (recombinant), inactivated-zhzo* with the proprietary name ANDEXXA, and International Nonproprietary Name (INN) *andexanet alfa*.

Portola proposed two dosing regimens for ANDEXXA. The low dosing regimen consists of an initial bolus of 400 mg followed by a 2-hour infusion of 480 mg of the product, totaling 880 mg. The high dosing regimen consists of an initial bolus of 800 mg followed by a 2-hour infusion of 960 mg, totaling 1760 mg. The safety and effectiveness of longer and higher doses, or repeat treatment with ANDEXXA have not been evaluated.

The active ingredient of ANDEXXA is a genetically modified variant of human coagulation Factor (F) Xa produced by recombinant DNA technology in a Chinese

Hamster Ovary (CHO) cell line. ANDEXXA was designed to bind small-molecule anticoagulant drugs that inhibit FXa, e.g., rivaroxaban and apixaban. ANDEXXA, unlike FXa, is unable to cleave prothrombin. ANDEXXA exerts its procoagulant effect by binding and sequestering FXa inhibitors rivaroxaban and apixaban. Another procoagulant effect of the ANDEXXA protein was observed, and is attributed to its ability to bind and inhibit the activity of Tissue Factor Pathway Inhibitor (TFPI).

Portola is conducting a program to demonstrate reversal of the anticoagulant effect of direct FXa inhibitors as measured by an anti-FXa activity assay in patient plasma. Portola proposed that the reduction of anti-FXa activity by ANDEXXA is reasonably likely to predict clinical benefit, and could be used as a surrogate endpoint in clinical studies. Controlled pre-licensure clinical studies using clinical endpoints, such as cessation of bleeding or decrease in bleeding-associated mortality, were deemed not feasible. FDA agreed with this proposal, and determined that an *Accelerated Approval* pathway would be appropriate for a BLA for the reversal of anticoagulation with direct FXa inhibitors.

2. BACKGROUND

ANDEXXA was developed to address an unmet medical need for patients treated with direct FXa inhibitors when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. These small-molecule drugs bind FXa and inhibit FXa activity directly, without the involvement of antithrombin III. In the United States (U.S.), these FXa inhibitor products are approved for the prevention of stroke in patients with nonvalvular atrial fibrillation, prevention of deep vein thrombosis (DVT) in hip or knee replacement surgery, and treatment and secondary prevention of venous thromboembolism (VTE) including DVT. These direct oral FXa inhibitors, together with direct oral thrombin inhibitors, belong to a class of anticoagulants known as direct oral anticoagulants (DOACs) or novel oral anticoagulants (NOACs). Since the approval of the first product in 2010, DOACs have been adopted rapidly reaching 4.21 million treatment visits in 2014, matching the use of the older oral anticoagulant drugs, such as vitamin K antagonists¹.

Direct FXa inhibitors are associated with an increase in bleeding events, some of which are life-threatening or fatal. There are no products licensed for the reversal of these direct FXa inhibitors. Administrations of Prothrombin Complex Concentrates (PCCs), activated PCC, or recombinant activated Coagulation Factor VII (rFVIIa) are currently used off-label for emergency care of patients receiving direct FXa inhibitors^{2,3,4}.

¹ Barnes GD et al. National Trends in Ambulatory Oral Anticoagulant Use. *Am J Med.* 2015 Dec;128(12):1300-5.e2.

² Eikelboom JW et al. Emergency care of patients receiving non-vitamin K antagonist oral anticoagulants. *Br J Anaesth.* 2018 Apr;120(4):645-656

³ Tomaselli GF et al. 2017 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol.* 2017 Dec 19;70(24):3042-3067

⁴ Majeed A et al. Management of rivaroxaban- or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood.* 2017 Oct 12;130(15):1706-1712

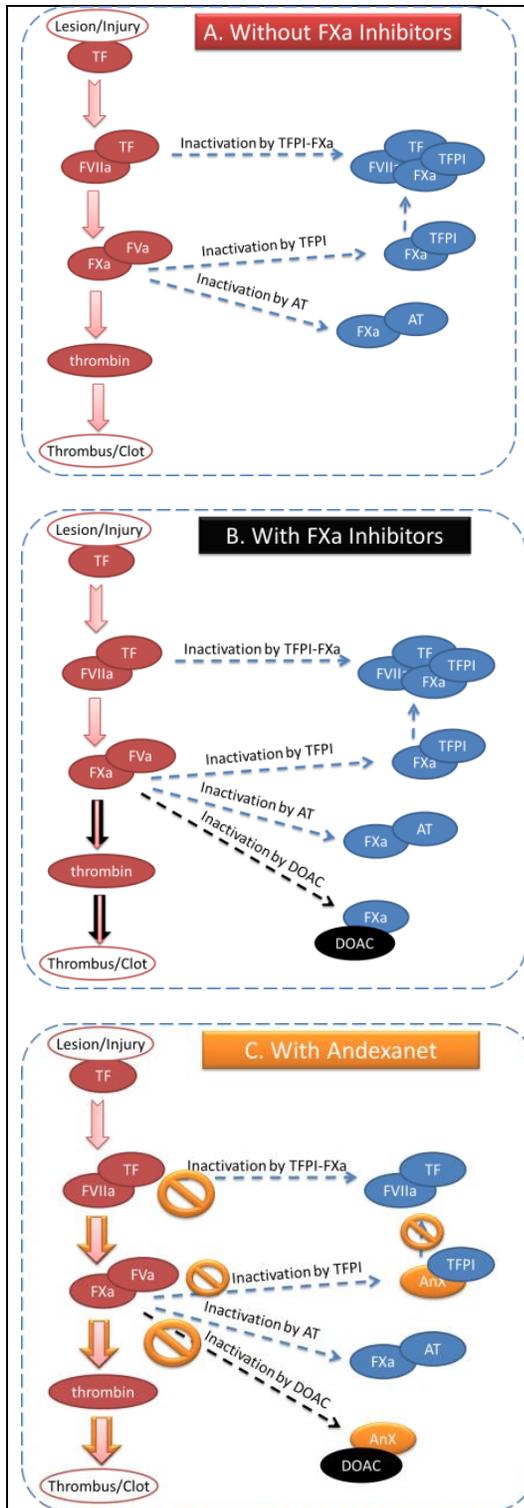


Figure 1: Mechanisms of action of direct FXa inhibitors and ANDEXXA.

A. Coagulation process without FXa inhibitors and ANDEXXA. Coagulation is initiated by exposure of Tissue Factor (TF) at the site of a vascular lesion followed by the formation of the TF-FVIIa complex (extrinsic FX-ase), activation of FX by TF-FVIIa (i.e., FXa generation), formation of FXa-FVa (prothrombinase complex) and activation of prothrombin to generate thrombin. Thrombin activates platelets and fibrinogen to fibrin, which leads to a hemostatic plug or thrombus formation. This process is inhibited by TFPI and antithrombin III (AT). TFPI inhibits FXa and TF-FVIIa in two stages: first, TFPI binds FXa to form a TFPI-FXa complex, and second, to form a stable inactive complex of TFPI-FXa-FVIIa-TF.

B. Direct Oral Anticoagulants (DOACs) rivaroxaban and apixaban facilitate FXa inhibition leading to reduced thrombin generation and reduced thrombus formation.

C. ANDEXXA (AnX) blocks rivaroxaban and apixaban leading to restoration of thrombin generation. In addition, AnX inactivates TFPI preventing its inhibition of TF activity. This leads to elevated TF-activated generation of FXa and thrombin.

Portola designed ANDEXXA to bind to the direct FXa inhibitors. FXa inhibitors reduce the ability of FXa to activate prothrombin to thrombin (Figure 1B). Similar to FXa, ANDEXXA forms a 1:1 inactive complex with FXa inhibitors leading to their sequestration from plasma. ANDEXXA lacks the FXa catalytic activity due to the

replacement of the active site serine with alanine, and is, therefore, unable to cleave and activate prothrombin. ANDEXXA also lacks the γ -carboxyglutamic acid (Gla)-containing domain of FXa, thus preventing its incorporation into the prothrombinase complex. The lack of interference in the formation of the prothrombinase complex is important for normal thrombin generation because the prothrombinase complex is ~300,000 fold more active than FXa alone in the activation of prothrombin to thrombin. Treatment with ANDEXXA is designed to reduce the concentration of FXa inhibitors, which should result in the restoration of normal thrombin generation needed to stop bleeding (Figure 1C).

ANDEXXA's second mechanism of action, binding and inactivation of TFPI, may also contribute to its procoagulant and/or thrombogenic activity. TFPI is the only known inhibitor of tissue factor (TF) which is a transmembrane glycoprotein responsible for the initiation of thrombin generation at the site of vascular lesions. Activation of coagulation starts with the formation of a complex between TF and FVIIa. The TF-FVIIa complex activates FX to FXa. TF-mediated activation of coagulation is down-regulated by the formation of TFPI-FXa complex, which leads to the formation of an inhibitory quaternary complex of TF, FVIIa, FXa and TFPI, thereby inhibiting coagulation. Like FXa, ANDEXXA binds TFPI, but the absence of the Gla domain prevents the formation of the inactive quaternary complex⁵, rendering the TFPI inactive. The result is the acceleration of the generation of FXa and thrombin⁶ (Figure 1C), which would promote thrombosis.

Regulatory history

The product is being developed in the U.S. under an Investigational New Drug application (IND 15089) for the proposed indication in patients who use FXa inhibitors when reversal of anticoagulant effect is needed due to serious uncontrolled bleeding events, or urgent or emergency surgery. ANDEXXA, if approved, will be the first recombinant FXa product, and the first product indicated for the reversal of the FXa inhibitors, rivaroxaban and apixaban.

On November 22, 2013, ANDEXXA received *Breakthrough Therapy* designation under IND 15089. On February 23, 2015, ANDEXXA also received *Orphan* designation for the proposed indication of “*reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event* (b) (4) ”.

The BLA was submitted as a rolling review. The Nonclinical sections in Module 2 (2.4 and 2.6) and Module 4 were received on November 6, 2015. The remaining Modules 1, 2, 3 and 5 were received on December 17, 2015. The original application was reviewed under a *Priority Review* schedule, and subject to PDUFA V requirements.

⁵ Marlu R & Polack B. Gla-domainless factor Xa: molecular bait to bypass a blocked tenase complex. *Haematologica* 2012 Aug;97(8):1165-72

⁶ Patent WO 2014116275 A1 “Inhibition of tissue factor pathway inhibitor with factor Xa derivatives”. Publicly available source: <https://patentscope.wipo.int/search/en/detail.jsf?docId=WO2014116275>

The BLA was submitted in accordance with 21 CFR, Part 601.40, Subpart E *Accelerated Approval of a Biological Product for a Serious or Life-threatening Illness*. The data used to support *Accelerated Approval* came from 5 pharmacokinetic (PK) and pharmacodynamic (PD) studies of healthy volunteers in which the reversal of anti-FXa activity was used as a surrogate endpoint. In these studies, an anti-FXa activity assay was used to measure the concentration of FXa inhibitors in plasma. Because the concentration of FXa inhibitor has been shown to correlate with its anticoagulant action, Portola proposed that the reduction of anti-FXa activity by ANDEXXA is reasonably likely to predict clinical benefit, and could be used as a surrogate endpoint in clinical studies.

In the healthy volunteer studies, a short-term transient reversal of anti-FXa activity, and a more sustained inactivation of the TFPI activity, were observed. Portola also submitted the results from an ongoing single-arm Phase 3b/4 clinical study in the intended patient population, but the preliminary results were not conclusive. Portola also agreed to conduct a Usual Care Cohort (UCC) in bleeding patients receiving direct FXa inhibitors in which the subjects could receive any commercially available product prescribed by the investigators.

During the first review cycle, CBER reviewers found significant deficiencies in the Chemistry, Manufacturing and Controls (CMC) and clinical information, which resulted in the issuance of a *Complete Response Letter* (CRL) to Portola on August 17, 2016. Deficiency of the UCC study protocol and insufficient clinical data to support the proposed indications were also included in the CRL.

On August 3, 2017, Portola responded to the CRL with additional CMC and clinical information. On December 18, 2017, Portola submitted a BLA amendment containing revisions to the safety data related to thrombotic events. The data presented in this amendment were part of a series of amendments, submitted between October 16 and December 1, 2017, that were meant to provide the clinical data needed by the FDA to complete the risk assessment in relation to the CRL. On December 22, 2017, FDA determined that the December 18, 2017 submission was a major amendment, because it contained a substantial amount of new data not previously submitted to, or reviewed by the Agency, that added an additional three months to the review clock. Therefore, the action due date was changed to May 4, 2018.

The new data from bleeding patients in the ongoing Phase 3b/4 study indicated that the changes in anti-FXa activity do not necessarily predict the clinical outcomes, while the risk of thrombosis in these patients was elevated. Therefore, FDA recommended that Portola amend the clinical program with a Randomized Control Trial (RCT) to evaluate ANDEXXA's clinical benefit versus the available standard of care.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

Manufacturing Process

The ANDEXXA Bulk Drug Substance (BDS) is manufactured at (b) (4) in (b) (4); and the Final Drug Product (FDP) at (b) (4) in (b) (4).

Bulk Drug Substance

The recombinant FXa variant of ANDEXXA, *coagulation factor Xa (recombinant), inactivated-zhzo*, is expressed in a CHO cell line, (b) (4).

Upstream processes of ANDEXXA BDS manufacture consist of (b) (4).

Downstream processes consist of viral inactivation (b) (4).

. The BDS is then formulated into FDP, (b) (4) sterile filtered, and filled into (b) (4) with a target volume of (b) (4).

Final Drug Product

(b) (4) BDS batches are used to manufacture one batch of FDP which may consist of approximately (b) (4) vials, sufficient to deliver an approximate (b) (4) low doses or (b) (4) high doses. There is a (b) (4). ANDEXXA is provided as a sterile, non-pyrogenic, white to off-white lyophilized cake in single-use glass vials, each containing about 100 mg of the recombinant protein. After reconstitution with 10 mL of sterile Water for Injection (sWFI), ANDEXXA forms a clear, colorless solution of the following composition: 100 mg (10 mg/mL) coagulation factor Xa (recombinant), inactivated-zhzo, 12.2 mg tromethamine, 94.8 mg L-arginine hydrochloride, 200 mg sucrose, 500 mg mannitol, and 1 mg polysorbate 80. sWFI is not provided with ANDEXXA.

Container Closure System

The drug product is filled into a 20-mL clear USP (b) (4) glass vial with a 20-mm finish ((b) (4)) and stoppered with a gray 20-mm (b) (4) and (b) (4) chlorobutyl rubber stopper ((b) (4)).

(b) (4)). The vial with stopper is capped with a 20-mm aluminum flip-off seal with a blue polypropylene flip-off cap (b) (4)). (b) (4) conducted the container closure integrity testing on the vials using a (b) (4) method; all acceptance criteria were met.

Manufacturing process development

Portola has thus far used (b) (4) manufacturing processes to produce ANDEXXA (b) (4) at the (b) (4) scale. (b) (4) was the GMP process to produce the (b) (4) FDP batches used in clinical trials. The subsequent (b) (4) included the (b) (4) in the final formulation so that the (b) (4) could be (b) (4) to 10 mg/mL during FDP manufacture. BDS (b) (4) used the (b) (4) . (b) (4) FDP batches were produced and used to support the Phases 2 and 3 trials with healthy volunteers. BDS (b) (4) is the current commercial manufacturing process. The most significant changes from BDS (b) (4) to (b) (4) are the introduction of the (b) (4) . BDS (b) (4) also incorporates the final (b) (4) steps using the FDP (b) (4) , instead of it being part of the FDP process.

The FDP manufacturing process has been changed (b) (4) concurrent with the respective changes in the BDS manufacture from (b) (4) . The FDP of (b) (4) was presented as a (b) (4) . (b) (4) introduced a lyophilized dosage form formulated at higher concentration (10 mg/mL) with mannitol manufactured at (b) (4) . The FDP of (b) (4) used the same formulation as (b) (4) , but is manufactured at an approximately (b) (4) in scale than (b) (4) , at the new FDP contract manufacturer, (b) (4) in (b) (4) .

Only (b) (4) materials were used in the pivotal Phase 3 clinical studies intended to provide evidence to support the ANDEXXA BLA through the *Accelerated Approval* pathway. (b) (4) materials were introduced in the ongoing confirmatory Phase 3b/4 clinical study in February 2016.

In-Process Controls

In-process controls (IPC) for the commercial process were developed using a risk-based approach to ensure the consistency of the manufacturing process and product quality. Portola proposed IPC parameters that are most likely to affect product quality attributes. The limits for the IPC parameters were based on prior manufacturing experience rather than prospective process optimization studies, which are normally done to define the edge-of-failure boundaries for critical and non-critical IPC parameters.

Process Performance Qualification

Process Performance Qualification (PPQ) covers the two major stages of production - BDS (b) (4) PPQ batches) and FDP (2 PPQ batches). Although the data support a successful PPQ, Portola experienced several deviations post-PPQ, which resulted in the

development of two new IPCs and adjustment of the existing IPC limits. These changes were validated to demonstrate adequate control over the manufacturing process.

In addition to the PPQ studies, several ancillary validation studies were performed to support the consistency of the manufacture of ANDEXXA BDS. The studies included the validation of (b) (4) [REDACTED], as well as *Shipping Qualification*.

Portola developed Continued Process Verification (CPV) plans for both (b) (4) [REDACTED] and (b) (4) [REDACTED] to ensure that the ANDEXXA manufacturing processes are in a state of control throughout the product lifecycle.

Potency

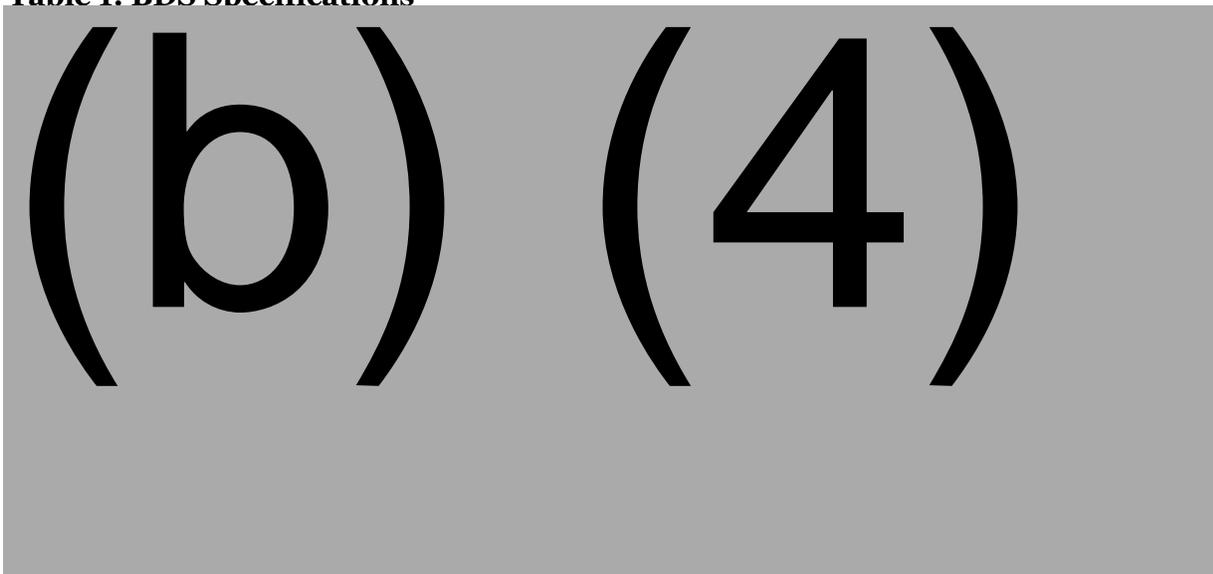
ANDEXXA is dosed by mass; therefore, it is important to establish a meaningful potency assay to assess the structure and function of the protein for the control of manufacturing process, product quality, and dosing consistency. Three assays were developed for the activity of ANDEXXA based on its inhibition of the effects of the (i) direct FXa inhibitor, (ii) indirect FXa inhibitor, and (iii) TFPI. In all three assays, the remaining FXa activity is measured by a FXa-specific (b) (4) [REDACTED]. The potency of ANDEXXA is determined by comparing the response of the test sample to that of the reference standard.

The assay for the reversal by ANDEXXA of the activity of direct FXa inhibitor is relevant to the biomarker, anti-FXa activity. Its reversal was proposed as the reasonably likely surrogate endpoint in the Phases 1, 2, and 3 clinical studies.

Release specifications

The specifications of BDS and FDP are summarized in Tables 1 and 2 below. The methods and specifications are established based on manufacturing experience and theoretical safety considerations.

Table 1: BDS Specifications



(b) (4)

(b) (4)

Table 2: FDP Specifications

Test Method	Parameter monitored	Acceptance Criteria
<i>Tests Performed on Lyophilized Product:</i>		
Visual Appearance	Characteristics	White to off-white lyophilized cake
Reconstitution Time	Characteristics	(b) (4)
Moisture Content per (b) (4)	Characteristics	(b) (4)
<i>Tests Performed on Product after Reconstitution with sWFI</i>		
Sterility ^a per (b) (4)	Purity	Sterile
Endotoxin per (b) (4)	Purity	(b) (4)
Appearance after Reconstitution	Characteristics	Clear, colorless to slightly yellow solution, essentially free from visible particulates
pH per (b) (4)	Characteristics	(b) (4)
(b) (4)	Characteristics	(b) (4)
Sucrose Content	Characteristics	(b) (4)
Mannitol Content	Characteristics	(b) (4)
Polysorbate 80 Content	Characteristics	(b) (4)

Test Method	Parameter monitored	Acceptance Criteria
Direct Potency	Identity and Potency	(b) (4)
Indirect Potency	Potency	
(b) (4) by TFPI Inhibition	Potency	
Protein Concentration by (b) (4)	Potency	
Purity by (b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	(b) (4)	
(b) (4)	Purity	
Particulate Matter per (b) (4)	Purity	
(b) (4)	(b) (4)	

Abbreviations and Notes:

(b) (4)
^a Sterility per (b) (4) is performed for batch release. Container closure integrity testing per (b) (4) is performed instead of the (b) (4) sterility test at annual stability time points.
^{(b) (4)}

Analytical Methods

Release methods were validated for their suitability for the intended use. The results of in-support testing for potency of the FDP were within the proposed specifications.

Elucidation of Structure and Product-Related Impurities and Substances

ANDEXXA is expressed in CHO cells as a functional protein, i.e., it does not require either *in vitro* or *in vivo* cleavage of the activation peptide, which is necessary for converting native FX to its activated form FXa. This is accomplished by the (b) (4) of coagulation factor Xa (recombinant), inactivated-zhzo. (b) (4)

(b) (4). ANDEXXA has (b) (4) amino acid residues and an approximate molecular weight of 41 kDa based on the cDNA sequence. Portola submitted data to confirm the primary, secondary, and higher order structures of ANDEXXA.

At least (b) (4) variants have been identified in ANDEXXA. They result from (b) (4)

[REDACTED]

The dominant truncated and full-length ANDEXXA species were purified and shown to be functionally active by the direct and indirect potency assays. The remaining protein variants are expected to be functionally active as well because they have the same active site domain needed for binding to the FXa inhibitors.

Characterization of Process-Related Impurities

The safety of process-related impurities in the FDP are evaluated in clinical studies, and the levels at which they are present have not been directly associated with adverse events. These impurities are derived from the cell line, cell culture medium, and materials used in the purification process. Risk assessment considered the number and capacity of the purification steps, amount per one (b) (4)-g dose (a conservative estimate above the maximum dose of 1760 mg that would be administered to a patient), toxicological risk of the potential impurities, and information in the literature.

Evaluation of Safety Regarding Adventitious Agents

For non-viral adventitious agents including bacteria, fungi, and mycoplasma, the potential of contamination of these agents is well controlled through the use of: (1) appropriate environmental monitoring in the manufacturing process; (2) in-process controls, e.g., (b) (4); and (3) filtration steps including (b) (4) sterile filtration. The potential of ANDEXXA to be contaminated with non-viral adventitious agents is further reduced by testing the FDP for sterility, endotoxins, and particulate matter. Portola and its contract manufacturers manufacture ANDEXXA according to GMP regulations.

No human- or animal-derived raw materials are used in the manufacture of ANDEXXA. No raw materials or ingredients of human or animal origin are used in the formulation of ANDEXXA FDP. Thus, the potential risk of adventitious viruses or transmissible spongiform encephalopathy (TSE) agents is minimized.

The potential for contamination by viruses in cell culture is well controlled in the manufacture of ANDEXXA, which is produced in a genetically modified CHO cell line. (b) (4), a contract testing facility for Portola, performed viral testing on the (b) (4) for ANDEXXA that is consistent with the International Conference on Harmonisation (ICH) Q5A(R1) guideline. All test results for endogenous and adventitious viruses were negative except for the (b) (4)

. (b) (4) routinely tests the cell cultures for adventitious viruses and (b) (4) to ensure that these viruses are below the levels of detection of the assays.

Additionally, the potential risk of viral contamination of ANDEXXA is further mitigated through two dedicated, (b) (4) viral clearance steps: (b) (4)

. Portola has evaluated these viral clearance steps in (b) (4) studies using model viruses of a wide range of physico-chemical properties. These studies on the relevant steps resulted in the following overall log reduction factors, in parentheses, for these viruses: (b) (4)

. These results are supportive of the effectiveness of the manufacturing process in viral clearance.

Stability

Portola proposed that the BDS can be stored at (b) (4) for (b) (4), and the FDP can be stored at +2°C to +8°C for 24 months. Thus far, the available stability results support the proposal. The stability studies are ongoing.

b) CBER Lot Release

Under the provision described in Federal Register (FR) 58:38771-38773 and the 60 FR 63048-63049 publication (December 8, 1995), routine lot-by-lot release by CBER is not required for ANDEXXA because it is a well-characterized recombinant product.

c) Facilities review/inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of *coagulation factor Xa (recombinant)*, *inactivated-zhzo* are listed in the table below. The activities performed and inspectional histories are noted in the table and are further described in the paragraphs that follow.

Table 3. Manufacturing Facilities for Coagulation Factor Xa (Recombinant), Inactivated-zhzo

Name/Address	FEI number	DUNS number	Inspection/waiver	Results/Justification
(b) (4) _____ _____ _____ _____ <i>Manufacturing</i>	(b) (4)		Pre-License Inspection	CBER (b) (4) _____ VAI ORA (Team Biologics) (b) (4) _____ VAI
(b) (4) _____ _____ _____ _____ <i>Drug Product Manufacturing</i>			Waived	ORA (b) (4) _____ VAI
(b) (4) _____ _____ _____ _____ <i>Primary labeling and packaging</i>			Waived	ORA (b) (4) _____ NAI
(b) (4) _____ _____ _____ <i>Drug Product Release Testing</i>			Waived	ORA (b) (4) _____ NAI

CBER performed a Pre-License Inspection (PLI) of (b) (4) _____ from (b) (4) _____ and a Form FDA 483 was issued at the end of the inspection. The firm responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues have been satisfactorily resolved.

After the Pre-License Inspection of (b) (4) _____ performed in (b) (4) _____, ORA (Team Biologics) performed a surveillance inspection from (b) (4) _____. The inspection was classified as voluntary action indicated (VAI). All inspectional 483 observations were resolved.

ORA conducted a surveillance inspection of (b) (4) _____ from (b) (4) _____. The inspection was classified as voluntary action indicated (VAI). All inspectional 483 observations were resolved.

ORA conducted a surveillance inspection of (b) (4) _____ from (b) (4) _____. The inspection was classified as VAI. All inspectional 483 observations were resolved.

ORA conducted a surveillance inspection of (b) (4) from (b) (4). The inspection was classified as no action indicated (NAI).

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31 (c). FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

e) Product Comparability

ANDEXXA received *Breakthrough* designation in 2013. To accommodate accelerated clinical development and in anticipation of the demand, several process modifications were introduced, including changes in dosage presentation ((b) (4) to lyophilized powder), formulation, protein concentration of FDP from (b) (4) to 10 mg/mL, excipient concentrations, new facilities and scale-up of the (b) (4) FDP processes. To evaluate the impact of these changes on product quality and process performance, Portola conducted extensive comparability studies for the clinical-scale and commercial-scale processes and provided sufficient process and analytical data to demonstrate that the material used in clinical trials is representative of the material intended for commercial distribution. These studies included comparisons between:

1. BDS manufacturing (b) (4)
2. FDP (b) (4) materials
3. BDS and FDP (b) (4) materials

f) Significant CMC issues resolved during the BLA review

Deficiencies in process validation, comparability, and clearance of (b) (4) impurities: Portola addressed issues related to (b) (4) of process intermediates and BDS, which was the root cause behind the deficiencies in manufacturing robustness and product quality. Portola identified the (b) (4) as (b) (4) impurities, demonstrated clearance of these impurities in the manufacturing process, revised the process control strategy to control (b) (4), and validated the revised manufacturing process. The materials manufactured by the revised commercial (b) (4) were shown to be comparable to those derived from (b) (4) used in the clinical trials. The (b) (4) ANDEXXA variants are found to be functional, and controlled by the revised lot release assays and release specification limits.

Deficiencies in characterization of ANDEXXA potency standard: To ensure the consistency of the potency, stability, and quality of the ANDEXXA primary product-specific reference standard (PRS), Portola developed product-specific activity units relative to international reference standards to allow for traceability of the potency for the PRS.

Deficiencies in specifications: The release specifications of the (b) (4) FDP were not sufficiently justified, and lacked several important parameters to ensure product safety and efficacy. Portola has since validated (b) (4) additional lot release assays (*Identity by (b) (4) _____, Sucrose, Mannitol, Polysorbate 80, Potency by TFPI Inhibition, and Purity by (b) (4) _____*) and revised the release specifications based on data generated from the commercial manufacturing process.

Deficiencies in stability studies: Portola developed new and revised analytical methods to establish the stability of product manufactured by the proposed commercial process.

Inadequate assessment of risks in the comparability protocol to introduce production (b) (4) : A comparability protocol (CP) was submitted in the BLA to support the introduction of a new manufacturing suite at (b) (4) _____, and scale-up of the (b) (4) FDP manufacturing processes. However, repeated process failures at (b) (4) _____ demonstrated that the scope of the manufacturing changes was too broad and complicated for their implementation through a CP/CBE-30 pathway. Portola informed the FDA that (b) (4) _____ is no longer considered for future use, and withdrew the CP from the BLA.

Deficiencies in qualification of bioanalytical methods used in the clinical studies: Because of the deficiencies in the qualification of the assays used in the clinical studies, the magnitude and duration of the inhibition of TFPI activity by ANDEXXA were underestimated, while the action of anti-FXa reversal was overestimated. Additional assay qualification studies confirmed the role of the inhibition of TFPI activity by ANDEXXA in the elevation of thrombin generation, and demonstrated inhibition of TFPI activity in healthy volunteers treated with FXa inhibitors. Portola also developed immunogenicity assays to measure (b) (4) _____ ANDEXXA antibodies that inhibit activities of endogenous FX and FXa.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

General Considerations

The safety and activity of ANDEXXA were characterized in a nonclinical program that included *in vivo* proof-of-concept testing in rabbit liver laceration and rodent tail transection models, as well as *in vivo* pharmacokinetics (PK), and single and repeat-dose toxicity studies in rats and (b) (4) _____ monkeys (non-human primates, NHPs).

Nonclinical Findings

Pharmacology

The effects of ANDEXXA on the reversal of anticoagulation by direct and indirect FXa inhibitors were evaluated in mice, rats and rabbits. Pharmacology (proof-of-concept) studies were conducted in FXa inhibitor-induced anticoagulated rabbit liver laceration and rodent tail transection models to determine the effect of ANDEXXA on blood loss

and other pharmacodynamic markers (i.e. INR, prothrombin time (PT)) of anticoagulation. The FXa inhibitor-induced anticoagulated rats and rabbits were dosed intravenously with increasing doses of ANDEXXA prior to tail transection and liver laceration. ANDEXXA administration rapidly decreased blood loss, PT and activated partial thromboplastin times (aPTT) to within normal limits in both the rabbit liver laceration and tail transection models. The ANDEXXA-mediated reduction in blood loss correlated with a reduction in anti-FXa activity and unbound FXa inhibitor plasma levels immediately following bolus injection of ANDEXXA. Under the conditions tested, ANDEXXA effectively reversed FXa inhibitors, based on the mitigation of blood loss compared to the FXa inhibitor treatment group. There were no effects of ANDEXXA alone on the hematology profiles in rats as compared to baseline, and no serious adverse effects or evidence of thrombogenicity were reported.

Pharmacokinetics

Single-dose PK studies with ANDEXXA were conducted in (b) (4) monkeys (NHPs) and (b) (4) rats. The PK profile of ANDEXXA in NHPs showed a dose-dependent increase in the PK parameters measured (i.e., C_{max} , and AUC_{24}). The PK studies in NHPs and rats demonstrated that the volume of distribution was relatively short and the elimination half-life was longer.

A PK study in NHPs was conducted with ANDEXXA in combination with an approved direct FXa inhibitor, to establish the effect of the direct FXa inhibitor on the PK parameters of ANDEXXA. In the presence of the FXa inhibitor, the C_{max} and AUC of ANDEXXA at a lower dose were significantly increased compared to ANDEXXA alone; however, no significant differences were noted at a 5-fold higher dose of ANDEXXA. In rats, the PK profile of the FXa inhibitor when administered with ANDEXXA was examined. The rats administered the FXa inhibitor and ANDEXXA displayed a significant increase in the C_{max} and AUC of the total FXa inhibitor, but the unbound levels of FXa decreased.

Toxicology

There were no reported systemic or tissue pathologies in NHPs and rats dosed with a single intravenous injection of ANDEXXA at doses up to 60 mg/kg/day in the presence and absence of FXa inhibitors. A 14-day, repeat-dose toxicity study with ANDEXXA was conducted in NHPs; groups of animals were dosed two times a day, every three days, by bolus intravenous injection with ANDEXXA at doses up to 60 mg/kg/day. Based on the results of this study, ANDEXXA was well tolerated, with no findings indicative of systemic toxicity or adverse local tolerance findings. However, elevated thrombin-antithrombin complex (TAT) and D-Dimer levels were detected in plasma samples obtained from the NHPs.

Special Toxicology Studies

No animal carcinogenicity, *in vivo* mutagenicity, fertility, reproductive toxicity or teratogenicity studies were conducted with ANDEXXA. ANDEXXA is a recombinant modified human Factor Xa protein; animals receiving repeated doses of the product developed antibodies against ANDEXXA. Therefore, long-term, repeat-dose toxicity

studies, as well as the standard carcinogenicity bioassay (i.e., 2 years of daily ANDEXXA dosing in both rats and mice) were not feasible to conduct.

The standard battery of genotoxicity testing as recommended in the International Conference on Harmonisation (ICH) S2 guidance documents was not conducted with ANDEXXA because it is a protein, and as per the ICH S6 guidance on biotechnology-derived protein therapeutics these studies are not required.

Toxicologic Risk Assessment Analysis

A toxicological risk assessment analysis was also provided in this submission, and provides identification and safety qualification of the extractable and potential leachable substances from the components used in the ANDEXXA manufacturing process. The results of this risk analysis indicated that the levels of potential leachable or extractable impurities are acceptable, as they were significantly lower than the maximally allowed daily exposure levels identified from extensive clinical and nonclinical experience.

5. CLINICAL PHARMACOLOGY

The clinical pharmacology program consists of four pharmacokinetic (PK) and pharmacodynamic (PD) studies.

PHARMACOKINETICS:

Four pharmacokinetic studies were conducted to characterize the PK profile of ANDEXXA.

In healthy subjects, ANDEXXA has a terminal half-life ranging from (b) (4) hours and clearance ranged from 4 to 6 L/hour. ANDEXXA is not excreted in urine of healthy subjects. Age (young adults and elderly) and gender have no impact on the PK of ANDEXXA. Apixaban and rivaroxaban have no impact on the PK of ANDEXXA but ANDEXXA decreases the oral and renal clearance of apixaban and rivaroxaban by at least 60 to 70%.

PHARMACODYNAMICS:

Anti-FXa Activity (Post-ANDEXXA/Placebo): Administration of ANDEXXA resulted in a rapid (within 2 minutes after the end of bolus dose) decrease in apixaban and rivaroxaban activity relative to pre-dose values. Both the magnitude and duration of apixaban and rivaroxaban activity reversal were dose-dependent. The effect on mean anti-FXa activity was sustained (relative to placebo) when followed by a continuous infusion. However, immediately after the cessation of infusion, anti-FXa activity started rising and reached placebo levels in a dose-dependent manner (generally by 4 to 6 hours). There was a direct correlation between anti-apixaban and rivaroxaban activity and unbound plasma concentration of apixaban or rivaroxaban, indicating that the unbound fractions may be responsible for the FXa inhibition.

Thrombin Generation: Administration of ANDEXXA resulted in a rapid (within 2 minutes following completion of ANDEXXA bolus dose) elevation of thrombin generation above the pre-apixaban or pre-rivaroxaban levels. The magnitude and duration of thrombin generation restoration following ANDEXXA administration were dose-dependent.

Total and free Tissue Factor Pathway Inhibitor (TFPI) Antigen: There was a decrease (approximately 60%) in the mean values for total TFPI antigen immediately following the first bolus dose of ANDEXXA. TFPI values started to increase towards baseline levels after 3 hours post-dose and came back to baseline values by Day 10. The mean free TFPI values decreased immediately after ANDEXXA dosing (within 2 minutes) in a non-dose-dependent manner and remained below placebo levels through 24 to 48 hours after the ANDEXXA dose, returning to placebo level afterwards.

CONCLUSIONS: In healthy subjects, the effect of ANDEXXA on PD markers (anti-FXa activity and thrombin generation) was immediate (within 2 minutes following completion of ANDEXXA bolus dose) and dose-dependent. A similar effect of ANDEXXA was noted on TFPI but not in a dose-dependent manner. There was a linear positive relationship between unbound concentrations of apixaban and rivaroxaban and anti-FXa activity and a linear inverse relationship between unbound concentrations of apixaban and rivaroxaban and thrombin generation, indicating that binding of ANDEXXA to unbound concentrations of direct inhibitors would result in a reversal of anti-FXa activity and elevation of thrombin generation.

Bioanalytical method reviewer's comment:

After the commencement of the aforementioned clinical pharmacology studies, Portola submitted validation reports of the bioanalytical methods used in these studies. Based on these results, the review chairperson is providing below additional explanations on the data reported in these PK/PD studies for the TFPI and thrombin generation assays, from a bioanalytical method reviewer's perspective.

Effect of ANDEXXA on TFPI activity: In healthy volunteers who were not taking FXa inhibitors, TFPI activity was inhibited below the limit of detection of the assay within 2 minutes after the end of the bolus dose, consistent with the decline in TFPI antigen. The TFPI antigen assays' validation results showed that ANDEXXA interferes with the antigen (b) (4) assay because ANDEXXA competes with the (b) (4) capture anti-TFPI antibody, and reduces the (b) (4) readout. Because of the interference of ANDEXXA in the antigen (b) (4) assay, the antigen results are deemed not reliable, although they can be informative on the level of TFPI activity.

In healthy volunteers who were taking FXa inhibitors, a TFPI activity assay was not used, and the changes in TFPI activity were estimated through the changes in TFPI antigen assay. Complete inhibition of TFPI activity was maintained for 22 hours. Data on when TFPI activity would return to either the pre-ANDEXXA treatment level, or the normal range were not provided.

Changes in TFPI activity and antigen were not studied in the target population.

Role of TFPI inhibition in thrombin generation: To delineate the magnitude and duration of the contribution of TFPI inhibition on the elevation of thrombin generation, a side-by-side comparison has been performed between the TF-activated thrombin generation assay versus the contact-activated thrombin generation using an APTT reagent. Inhibition of TFPI by ANDEXXA contributed to the elevation of thrombin generation above the pre-FXa inhibitor baseline. TFPI inhibition was also responsible for the maintenance of thrombin generation level above the placebo level for at least 22 hours after ANDEXXA bolus.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

To support licensure of ANDEXXA, Portola submitted data from 6 prospective studies, including data from 349 healthy volunteer subjects treated with ANDEXXA or placebo in 5 studies, and data from 185 subjects experiencing acute major bleeds who received ANDEXXA for reversal (target population) from the ongoing ANNEXA 4 study. The clinical development program is summarized in the table below. All studies were performed under IND 15089; Phase 3 studies were reviewed under the breakthrough therapy designation program.

Table 4: Completed and Ongoing Clinical Studies

Trial ID (Type of Study)	Design	Subjects; Mean Age (range)	Anticoagulant Administration (n); Dose	ANDEXXA* (Dose)	Placebo
Phase 3 Studies					
14-503 Efficacy/ Safety	Single center, randomized, double-blind, placebo-controlled	N=65 healthy older subjects; 60 years (50–73)	Part 1: Apixaban (n=33) 5 mg orally every 12 hours for 3.5 days	n=24 400 mg bolus	n=9
			Part 2: Apixaban (n=32) 5 mg orally every 12 hours for 3.5 days	n=24 400 mg bolus followed by a 120 min infusion at 4 mg/min	n=8
14-504 Efficacy/ Safety	Single center, randomized, double-blind, placebo-controlled	N=80 healthy older subjects; 56 years (50–68)	Part 1: Rivaroxaban (n=41) 20 mg orally every 24 hours for 4 days	n=27 800 mg bolus	n=14
			Part 2: Rivaroxaban (n=39)	n=26	n=13

Trial ID (Type of Study)	Design	Subjects; Mean Age (range)	Anticoagulant Administration (n); Dose	ANDEXXA* (Dose)	Placebo
			20 mg orally every 24 hours for 4 days	800 mg bolus followed by a 120 min infusion at 8 mg/min	
ANNEXA 4/14-505 Efficacy/ Safety	Multicenter, open-label, single arm	Subjects with acute major bleeding (n=185) 78 years (55-95)	Apixaban (n=98) Rivaroxaban (n=72) Enoxaparin (n=14) Edoxaban (n=1)	Low dose: 400 mg bolus dose followed by 4 mg/min for up to 120 min High Dose: 800 mg bolus dose followed by 8 mg/min for up to 120 min	N/A

* Dose was based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the subject's last dose of FXa inhibitor

This BLA was reviewed under accelerated approval using the surrogate of anti-FXa activity. Under Section 506(c) of the Food, Drug and Cosmetic Act (FD&C Act), accelerated approval is reserved for products intended to treat or cure a “serious or life-threatening condition” based on surrogate endpoints that are “reasonably likely to predict clinical benefit.”

In the clinical development program for ANDEXXA, Studies 14-503 and 14-504 provided the primary evidence in support of the evaluation of safety and efficacy of the product. Data from the ongoing confirmatory study (14-505) provided supportive evidence for the evaluation of safety and effectiveness.

Data from a single Phase 2 study (12-501) was also included in support of efficacy data for reversal of anticoagulation in subjects who were treated with edoxaban and enoxaparin.

Study 12-502 was a dose-exploration Phase 2 study in which:

- 18 subjects who were treated with enoxaparin received ANDEXXA and 8 subjects who were treated with enoxaparin received inactive placebo treatment. Six subjects received 420 mg of bolus infusion only.
- 28 subjects who were treated with edoxaban received ANDEXXA and 8 subjects who were treated with edoxaban received placebo. Six subjects in the treatment arm received 800 mg followed by a one-hour infusion at 8 mg/minute of ANDEXXA.

The mean age of subjects who received ANDEXXA in the study of subjects treated with enoxaparin was 34 (Range: 21-45) years.

The mean age of subjects who received ANDEXXA in the study of subjects treated with edoxaban was 33 (Range 19-45) years.

The details of the study design and treatment will not be discussed in detail as these studies were not the primary studies intended to support the approval of ANDEXXA in the indication that it is being approved for. However, the rationale to limit the use of ANDEXXA such that enoxaparin and edoxaban are excluded from use will be discussed below in the discussion of the efficacy results.

Phase 3 Studies in Healthy Volunteers

- Trials 14-503 and 14-504 were conducted as randomized, double-blind, placebo (inactive)-controlled trials to demonstrate the ability of ANDEXXA to reverse anticoagulation of apixaban (Trial 14-503) or rivaroxaban (14-504) and evaluate the safety of ANDEXXA in older healthy volunteer subjects (aged 50–75 years). Subjects were dosed to steady-state with apixaban or rivaroxaban, followed by an ANDEXXA bolus that was started 3 (apixaban) or 4 (rivaroxaban) hours after the last anticoagulant dose (at the approximate steady-state maximum plasma concentration).
- Subjects anticoagulated with apixaban received the low-dose ANDEXXA regimen of 400 mg bolus or 400 mg bolus followed by a 120-minute infusion at 4 mg/min. Subjects anticoagulated with rivaroxaban received the high-dose ANDEXXA regimen of 800 mg bolus or 800 mg bolus followed by a 120-minute infusion at 4 mg/min.
- The primary objective of both studies was to compare the reversal of anticoagulation as measured by anti-FXa activity (surrogate marker) for ANDEXXA and placebo, 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 or rivaroxaban concentration at the +2 minute or +5 minute time point after the completion of the ANDEXXA bolus.

- Restoration of thrombin generation defined as change in thrombin generation from levels 1 day prior to edoxaban administration and levels following ANDEXXA bolus and infusion.

Subjects were followed for safety through Day 43. Subjects remained on study for approximately 8 to 12 weeks, depending on the length of screening.

Study Population and Disposition

For details of enrollment, randomization, treatment received and dose for Studies 14-503 and 14-504, please refer to the table above.

Study 14-503

In this study, subjects were treated with apixaban prior to treatment with ANDEXXA to observe for the change from baseline anti-FXa activity levels. The mean (SD) age of subjects in Part 2 was 59.4 (7.5) years (median of 56.5 years with a range of 50 to 73). One subject ((b) (6)) randomized to the ANDEXXA group was not included in the Efficacy Analysis (mITT) or per-protocol populations because study drug was discontinued partway through the infusion and the site did not collect follow-up blood tests on that day, as required for inclusion in the mITT population.

Study 14-504

In this study, subjects were treated with rivaroxaban prior to treatment with ANDEXXA to observe for the change from baseline anti-FXa activity levels. The mean (SD) age for subjects in Part 2 the mean age was 57.3 (5.16) years (median of 57 years with a range of 50 to 68). In part 2, two subjects in the ANDEXXA group did not complete the study:

- Subject (b) (6) withdrew from the study, underwent study procedures through Discharge Day 8 and an Early Termination Visit on Day 33.
- Subject (b) (6) was lost to follow-up and did not undergo any study procedures after Study Day 15.

Phase 3b/4 Ongoing Study (ANNEXA 4 Study/Study 14-505)

Study Design

Portola anticipated that the ANNEXA 4 study would serve as a confirmatory study, which is an ongoing multi-center, prospective, open-label, single-arm study of ANDEXXA in approximately 350 subjects (250 evaluable) presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. However, after review of the applicant's response to the Complete Response Letter, the review team determined that ANNEXA 4 would not be a required post-marketing study.

During the review of the original submission, FDA advised the applicant to a) increase the enrollment of subjects with intracranial haemorrhage in the

ANNEXA 4 study and b) include a prospective control cohort in which subjects were to be treated with usual care (UCC study). The recommendation was based on the adjudication issues with hemostasis outcomes in subjects with gastrointestinal and non-visible bleeding in the ANNEXA 4 study and the transient nature of reversal observed in both the healthy volunteer and the ANNEXA 4 studies. The applicant was also advised that anti-FXa activity level was not a suitable surrogate endpoint to evaluate the efficacy of enoxaparin given the dual pathway through enoxaparin exerts its anticoagulant activity. The ANNEXA 4 protocol was revised accordingly and the statistical analysis plan incorporated a comparison of hemostatic outcomes between the ANNEXA 4 study and the UCC study.

Endpoints

The study has co-primary efficacy endpoints:

- percent change from baseline in anti-FXa activity to the nadir during the evaluation period which begins 5 minutes following the end of the bolus and ends 10 minutes after the end of the infusion; and
- proportion of efficacy-evaluable subjects who are adjudicated to have effective hemostasis (excellent or good) by the independent endpoint adjudication committee (EAC).

Treatment

- Based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the subject's last dose of FXa inhibitor, subjects will receive either the low or high dose of ANDEXXA. The low dose is 400 mg i.v. bolus + 4 mg/minute infusion for 120 minutes and the high dose is 800 mg i.v. bolus + 8 mg/minute infusion for 120 minutes.
- Following the start of ANDEXXA treatment, subjects are evaluated for the study efficacy endpoints for 12 hours from the start of ANDEXXA bolus with clinical assessments for visible, muscular, and skeletal bleeding; head computed tomography (CT) and modified Rankin score (mRS) for intracranial haemorrhage; and transfusion-corrected hemoglobin and hematocrit for non-visible bleeding. Hemostatic efficacy is adjudicated by an independent EAC using a three-point rating scale (Appendix I) of excellent (effective), good (effective), or poor/none (not effective). The EAC also adjudicates all potential thrombotic events and are blinded to all anti-FXa levels.
- The study duration for any individual subject will be up to 37 days. For subjects discontinued early from the study, the study duration is when early termination visit is completed:

Study Population and Disposition

The applicant included data from 185 subjects who received at least one dose of ANDEXXA as of the analysis cut-off date of April 20, 2017 for this resubmission. The indication that the applicant is seeking is for treatment patients who were treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. The ANNEXA 4 study

enrolled a limited number of subjects who were treated with enoxaparin (n=14) or edoxaban (n=1); therefore, the population for discussion of efficacy is identified as subjects who experienced bleeding from apixaban or rivaroxaban.

- Safety evaluable population: any subject who received one dose of ANDEXXA (n=185).
- Per the protocol, the efficacy-evaluable population: any subjects in the safety-evaluable population who were treated with apixaban or rivaroxaban, experienced life-threatening bleeding or uncontrolled bleeding adjudicated by the EAC, who had baseline anti-FXa levels > 75 ng/mL (as determined by the central laboratory) and had nadir anti-FXa levels available (n=98). The efficacy-evaluable population in the statistical analysis plan includes the definition as above but also includes subjects receiving edoxaban and enoxaparin in addition to apixaban and rivaroxaban (n=108). The efficacy outcomes were pending adjudication for the 108 subjects.

Efficacy Results

Phase 2 Study Results

Study 12-502

Efficacy results

Of the six subjects who received 800 mg bolus + 1-hour infusion regimen, the mean percent reduction from baseline to nadir in anti-FXa activity (depth of reversal) was 67%.

FDA did not accept the surrogate endpoint of anti-FXa activity levels as acceptable to demonstrate hemostatic efficacy of ANDEXXA in subjects anticoagulated with enoxaparin. Enoxaparin's mechanism of anticoagulant activity is based on its activity against factors Xa and IIa. Since Study 12-502 evaluated the effect of ANDEXXA solely on anti-FXa, this data was considered insufficient to support a marketing claim as a reversal agent for enoxaparin.

Clinical Reviewer Conclusions: The dose administered for reversal of edoxaban (1-hour infusion) was different from the dose administered for apixaban and rivaroxaban (2-hour infusion). In addition, the extent of reversal of edoxaban, as observed through anti-FXa activity levels, was substantially less than for apixaban and rivaroxaban. As noted above, the design of Study 12-502 was found insufficient with regard to enoxaparin reversal. For these reasons, during the review of the original submission, FDA determined that the data from Studies 12-502 were insufficient to support efficacy claims for ANDEXXA as a reversal agent for edoxaban and enoxaparin. In this submission (response to the CRL) the applicant does not plan to include an indication for reversal of edoxaban and enoxaparin. This issue has been adequately addressed. The limitations of use in the label notes that the safety and efficacy of ANDEXXA for treatment of life-

threatening bleeding in patients treated with edoxaban and enoxaparin has not been established.

Phase 3 Studies in Healthy Volunteers

Efficacy Results

Table 5: Change in Anti-FXa Activity in Studies 14-503 and 14-504

Anti-FXa Activity	Study 14-503 (apixaban)		Study 14-504 (rivaroxaban)	
	ANDEXXA n=23	Placebo n=8	ANDEXXA n=26	Placebo n=13
Mean % (± SD) change from baseline at the nadir	-92.34 (2.809)	-32.70 (5.578)	-96.72 (1.838)	-44.75 (11.749)
Hodges-Lehman estimate of shift (95% CI)	-59.50 (-64.10, -55.17)		-51.87 (-57.95, -47.03)	
p-Value	< 0.0001 ^a		< 0.0001 ^a	

SD = Standard deviation

^a p-Value obtained from a 2-sided exact Wilcoxon rank-sum test

Both studies reached statistical significance on the analysis of all primary and secondary efficacy endpoints: significant differences in anti-FXa activity reduction, free drug concentration, and restoration of thrombin generation were observed between subjects in the ANDEXXA and placebo groups.

Figure 2: Study 14-503, change in anti-FXa activity in subjects anticoagulated with apixaban

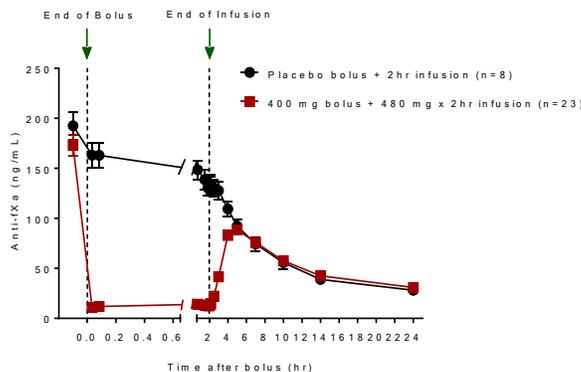
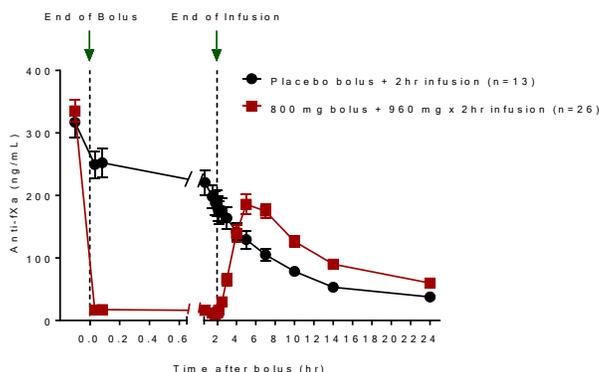


Figure 3: Study 14-504, change in anti-FXa activity in subjects anticoagulated with rivaroxaban



Study 14-503: Anti-FXa returned to levels observed in the placebo group within 300 minutes after the end of the bolus or bolus plus infusion (Figure 2). For both parts of the study, all subjects in the ANDEXXA group had $\geq 80\%$ reduction in anti-FXa activity.

Compared to placebo, subjects who received ANDEXXA had significant increases from baseline to its peak in endogenous thrombin potential (ETP), a biomarker of thrombin generation.

Study 14-504: Anti-FXa returned to levels observed in the placebo group within 120 minutes after the end of the bolus or bolus plus infusion (Figure 3).

All but one subject treated with ANDEXXA had $\geq 80\%$ reduction in anti-FXa activity, as compared to no subjects in the placebo group. Per the applicant, Subject (b) (6), enrolled in Part 1 of the study, had leakage of study drug from the infusion port and was noted to have undetectable ANDEXXA levels in the plasma at 2 minutes or 10 minutes following the bolus.

ETP from baseline to its peak increased significantly more in subjects who received ANDEXXA than in subjects who received placebo.

Clinical Reviewer Conclusions: Treatment with ANDEXXA was associated with a substantial percentage change from baseline to nadir anti-FXa activity levels. This change was observed almost immediately following the bolus infusion as noted in Figures 2 and 3. The durability of reversal (change from baseline to nadir in the anti-FXa levels) was transient at 300 minutes to reach levels comparable to placebo in Study 14-503 (apixaban) and 120 minutes to reach levels comparable to placebo in Study 14-504 (rivaroxaban).

Ongoing study - ANNEXA 4 study

The efficacy results presented below summarize the analyses and results of the anti-FXa levels in the ongoing ANNEXA 4 study. The UCC study has not been initiated yet and the discussion of the hemostatic outcomes and efficacy of ANDEXXA in the absence of control data will not be the focus of the review of the response to the complete response letter (CRL). Of the efficacy-evaluable population, 51% experienced an intracranial hemorrhage, 37% experienced gastrointestinal bleeding, and 12% experienced other bleeds (for example, intraspinal, pericardial, retroperitoneal).

The median nadir value and decrease from baseline to nadir in anti-FXa activity observed are summarized in Table 6 for subjects in the Efficacy Analysis Population. The 95% CIs provided were based on a non-parametric method. The results of enoxaparin are not presented due to the small number of subjects (n=2). Please note the total number of subjects do not add up to 108 because some subjects had missing nadir values.

Table 6: ANNEXA 4 Summary of change from baseline anti-FXa levels

FXa	N	Nadir value Median (95%CI)	Absolute change median (95%CI)	% change in median (95% CI)
All	99	11.1 (9.5, 13.5)	-147.4 (-161.7, -127.0)	-92.3% (-93.6%, -90.3%)
Apixaban	57	11.0 (8.6, 12.9)	-145.7 (-157.1, -117.7)	-92.6% (-93.8%, -91.4%)
Rivaroxaban	40	13.5 (9.1, 25.3)	-165.8 (-195.8, -137.8)	-90.6% (-93.8%, -86.7%)

Clinical Reviewer Conclusions: There are differences in the dosing in Studies 14-503 and 14-504, and the ANNEXA 4 study. Study 14-503 was based on administration of a low dose of ANDEXXA, while Study 14-504 was based on administration of a high dose of ANDEXXA. Despite these differences, the percent change in anti-FXa levels for rivaroxaban and apixaban in the ANNEXA 4 study are consistent with the results observed in Studies 14-503 and 14-504. ANDEXXA at the proposed doses, demonstrates sufficient evidence of a treatment effect on anti-FXa levels.

c) Pediatrics

This product received Orphan designation for the proposed indication of “reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in subjects experiencing a serious uncontrolled bleeding event (b) (4) [REDACTED]” on February 23, 2015; therefore, pediatric studies were not required. The safety and efficacy of ANDEXXA in the pediatric population has not been studied.

d) Other Special Populations

There is no information regarding the presence of ANDEXXA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANDEXXA and any potential adverse effects on the breast-fed infant from ANDEXXA or from the underlying maternal condition.

e) Bioresearch Monitoring

Bioresearch Monitoring (BIMO) inspections were conducted at four domestic clinical sites that participated in the conduct of Studies 14-503, 14-504 and 14-505. The inspections did not reveal any issues that impact the data submitted in this application.

7. SAFETY

Data from 4 studies in healthy volunteers; one Phase 1 study (Study 14-506), one Phase 2 (Study 12-502) and two Phase 3 studies (Studies 14-503 and 14-504) were pooled for safety analysis.

Data from the ongoing ANNEXA 4 study were not pooled as the population in this study is different from the population in the healthy volunteer studies. Subjects in the ANNEXA 4 study experienced life-threatening or major bleeding and were at greater risk of thrombo-embolic and ischemic risks from the underlying disease. Subjects in the healthy volunteer studies did not experience bleeding and were not at risk for thromboembolic or ischemic events.

Healthy Volunteer Studies

Please refer to the efficacy section for details of the demographic characteristics of Studies 14-503 and 14-504. In Study 12-502, 157 subjects were enrolled, 102 subjects received doses of ANDEXXA that ranged from 90 mg as a bolus dose to up to 1280 mg of ANDEXXA, and 50 subjects received placebo. In Study 14-506, all 20 subjects who were enrolled received ANDEXXA at a dose of 400mg (bolus only).

- No thromboembolic events were observed in 223 healthy volunteers who received FXa inhibitors and were treated with ANDEXXA. Elevations in biomarkers of pro-coagulant activity (D-dimer and prothrombin fragment 1+2) and inhibition of Tissue Factor Pathway Inhibitor (TFPI) activity were observed in subjects who were treated with ANDEXXA compared to subjects who received placebo.
- Infusion-related reactions occurred in 18% (39/223) of ANDEXXA-treated healthy volunteers vs. 6% (6/94) of placebo-treated subjects, and were

characterized by a range of symptoms including flushing, feeling hot, cough, dysgeusia, and dyspnea.

Clinical Reviewer Conclusions: The elevated markers, D-dimer and prothrombin fragment 1+2, and inhibition of TFPI activity are suggestive of procoagulant activity as these laboratory evaluations are considered biomarkers of a procoagulant state. The results of these laboratory parameters provide a biologically plausible reason for the higher than anticipated thrombo-embolic and ischemic risks observed in the ANNEXA 4 study (see below).

ANNEXA 4 study

Of the safety-evaluable population, 58% experienced intracranial hemorrhage bleeding, 31% experienced gastrointestinal bleeding and 11% experienced other bleeds. As noted above, subjects at a high-risk for mortality (Glasgow Coma Scale < 7 and intracerebral hemorrhage > 60cc) were excluded from the study. Eighty-seven percent (87%) of the subjects were older than 65 years of age and 52% of subjects were male. Fifty-three percent (53%) of subjects were anticoagulated with apixaban and 39% with rivaroxaban.

Adverse Events of Special Interest

Protocol-specified adverse events of special interest (AESI) were defined as acute myocardial infarction, deep venous thrombosis, pulmonary embolism, ischemic or embolic or unknown reasons for stroke. FDA included additional events in the assessment of AESI, as these events were suggestive of ischemic or thromboembolic events; these included cardiac arrest, cardiac thrombus, iliac artery occlusion, cardiogenic shock, congestive heart failure, ventricular tachycardia and acute respiratory failure, for which alternate explanations could not be provided. For safety analyses, the FDA-assessed AESI (FDA-AESI) will be included for discussion purposes.

A summary of the key adverse events are provided below:

Table 7: FDA-AESI

AESI (total number of subjects - 185)	Number of events*	Female (n=15)	Male (n=18)
Acute myocardial infarction*	5	2	3
Acute respiratory failure	2	2	0
Cardiac arrest	1	0	1
Cardiac thrombus	1	1	0
Cardiogenic shock	3	2	1
Congestive heart failure	2	0	2
Deep venous thrombosis*	11	5	6
Embolic Stroke*	1	1	0
Iliac artery occlusion	1	0	1

AESI (total number of subjects - 185)	Number of events*	Female (n=15)	Male (n=18)
Ischemic stroke*	8	4	4
Pulmonary embolism*	5	2	3
Sudden cardiac death	1	0	1
Sudden death	1	0	1
Ventricular tachycardia	1	1	0
Total number of AESI events	43	20	23

43 FDA-AESI occurred in 33 subjects

*Protocol-specified AESI

The percentage of safety-evaluable subjects experiencing a thrombo-embolic or ischemic event (FDA-AESI event) was 17.8%. Of the 43 FDA-AESI events, 16.9% occurred in subjects with intracranial bleeding and 24% occurred in subjects with GI bleeding. The median time to the first event in these 33 subjects was 6 days.

Of the 86 patients who were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic, ischemic event, cardiac event or death.

Clinical Reviewer Conclusion: The 17.8% rate of thrombo-embolic and ischemic events in the ANNEXA 4 study is higher than anticipated for subjects with underlying risks of thrombo-embolism or ischemic events in whom anticoagulation is reversed. The proportion of subjects with intracranial hemorrhage who developed a thrombo-embolic or ischemic event was lower than with gastrointestinal bleeding. Re-initiation of anticoagulation (re-anticoagulation) in subjects who were medically fit for re-anticoagulation, lowered the rate of the thromboembolic and ischemic events. However, these risks appear to be higher than anticipated in the population despite re-initiation of anticoagulation.

Deaths

There were no deaths in the healthy volunteer studies. In the ANNEXA 4 study, the all-cause mortality rate during the 37-day observation period (range: 1-44 days) was 13.5%. Of the 25 subjects who died, 60% experienced intracranial hemorrhage and 24% experienced gastrointestinal bleeding. The median time to death after ANDEXXA infusion was 16 days (range: 1 to 44 days), with 8 deaths occurring within 10 days after the infusion.

Clinical Reviewer Conclusion: 58% of subjects with intracranial hemorrhage represent the safety-evaluable population. The percentage of patients by bleeding type who died prior to the Day 30 follow-up visit was 14% for intracranial bleeding, 10% for gastrointestinal bleeding, and 19% for other bleeding types. In general, intracranial hemorrhage related bleeding is the leading cause of the mortality following oral anticoagulant-related bleeding. However, the results of the all-cause mortality should be interpreted with caution as the study excluded subjects at high-risk for mortality.

Overall Safety Conclusions

- The rate of thromboembolic events, ischemic events, cardiac arrest and sudden death is 17.8%. Although re-anticoagulation decreased the rate of these events, the rate of thromboembolic events of 10.5% following re-anticoagulation remains a safety concern.
- These observations were supported by the elevation in biomarkers of pro-coagulant activity such as elevated D-dimers and prothrombin fragment 1+2, inhibition of TFPI, and elevated thrombin generation.
- The 30-day mortality is within the anticipated rates for the population, noting that the study enrolled subjects at lower risk of death.

8. ADVISORY COMMITTEE MEETING

The application was not referred to the Blood Products Advisory Committee because senior leadership in the product office and center determined that a decision regarding the information submitted in the BLA, including the clinical study design and trial results, would not likely have benefited from additional discussion at an advisory committee.

9. OTHER RELEVANT REGULATORY ISSUES

This application is not affected by the Application Integrity Policy. The notable clinical issues raised during the review are described in the respective sections of this document. The clinical issues, items 1 and 2 were considered substantial review issues resulting in internal and external disagreements.

A. Internal and external disagreements regarding clinical issues

1. Concerns that anti-FXa activity reversal can reasonably likely predict clinical benefit

Per the 2014 Guidance on Expedited Programs for Serious Conditions, FDA must review the evidence provided in the BLA that a proposed surrogate endpoint is reasonably likely to predict the intended clinical benefit of a drug. During review of Portola's IND and BLA, FDA reviewers expressed concerns regarding the evidence supporting the use of anti-FXa activity as the PD biomarker to support ANDEXXA approval, and the strength of the evidence supporting the ability of the marker to predict clinical benefit.

Although reduction of inhibitor activity below the pharmacologically active level can be viewed as reasonably likely to predict the clinical outcome related to reversal of anticoagulation, Portola was not able to demonstrate the minimally sufficient pharmacologically level below which the inhibitors, rivaroxaban and apixaban, are not active in bleeding subjects. Anti-FXa activity reflects the drug concentration but do not reflect the drug's

anticoagulant activity. As noted in the FDA Guidance for Expedited Programs, evidence of pharmacological activity alone is insufficient to support a conclusion that a relationship of an effect on a surrogate endpoint to the effect on a clinical outcome is reasonably likely. Consultative opinions were obtained during the review of the original submission from FDA's clinical review divisions external to CBER with expertise in anticoagulation and reversal agents for anticoagulants. The opinions of these review divisions were consistent with concerns raised by CBER reviewers regarding suitability of anti-FXa activity as a surrogate endpoint reasonably likely to predict a clinical benefit of hemostasis.

In the efficacy-evaluable population of 106 subjects who received ANDEXXA for treatment of bleeding related to apixaban and rivaroxaban, the change from baseline to nadir anti-FXa activity was similar in the subjects who achieved excellent/good (n=90) and poor/none (n=16) hemostatic responses. In addition, in some subjects with anti-FXa levels well above the 75 ng/mL cut-off of anti-FXa activity considered by the applicant to represent therapeutic levels of anticoagulation, mean % change in baseline levels did not correlate with hemostatic outcomes. For example, in 38 subjects who had baseline anti-FXa activity levels between 150-299 ng/mL, 30 subjects achieved excellent to good outcomes and 8 subjects achieved poor/none hemostatic outcomes. However, the mean % change from baseline to nadir anti-FXa levels were similar in both groups. This observation raised concerns within the review team that correlation in support of anti-FXa activity as a surrogate endpoint reasonably likely to predict for hemostatic outcomes is yet to be demonstrated.

2. Insufficient data to assess benefit-risk of ANDEXXA

In the absence of sufficient data to demonstrate that the change from baseline to nadir anti-FXa activity levels are reasonably likely to predict for hemostatic outcomes, assessment of the benefit in the context of the thrombo-embolic and ischemic risks are particularly challenging.

A direct comparison of historical data of hemostatic outcomes may not be used for regulatory decision but puts into perspective a treatment option and outcomes of therapeutic options that may be available to the population at risk. The observed rate of hemostasis was 69.1% in a prospective single-arm study by Majeed et al (Blood, 2017) of 84 patients who experienced bleeding from rivaroxaban and apixaban and received 4-factor PCC. Approximately 73% of patients with intracranial hemorrhage (risk-based exclusion of patients as an eligibility to the study was not noted in this study) experienced favorable hemostatic outcomes. The 30-day mortality rates were 32%, with 67% of these deaths due to bleeding and 26% of these deaths from sepsis and multi-organ failure. Over a 30-day period post-treatment, three patients (3.5%) were confirmed or suspected to have a thromboembolic event and one subject developed a cardiac arrhythmia and arrest (1.1%).

B. Other issues

3. Incomplete investigation of anti-TFPI action & risk of thrombosis

Throughout its communications with FDA all the way to the BLA, Portola has claimed that ANDEXXA has no pro- or anti-coagulant activity. During the review of the BLA, clinical reviewers expressed concerns about the potential risk of thrombogenicity arising from the elevated thrombin generation noted in subjects. In response to these concerns, Portola acknowledged that the increased thrombin generation can be explained by the effect of ANDEXXA on TFPI activity. Additional studies requested in the CRL have confirmed this conclusion. Furthermore, re-analysis of TFPI activity and antigen assay data demonstrated that ANDEXXA completely inhibits TFPI for at least 22 hours. Because TFPI inhibition by ANDEXXA elevates markers of thrombogenicity, and this effect is not as transient as anti-FXa activity reversal, it is necessary for health care providers to be aware of the duration and magnitude of both mechanisms of action of ANDEXXA. However, the time from decrease following ANDEXXA treatment to increase to pre-ANDEXXA levels of TFPI activity was not determined.

4. Pharmacological class

Portola proposed to use the adopted USAN name, *andexanet alfa*, for the proper (non-proprietary) name of ANDEXXA. FDA assigned the proper name *coagulation factor Xa (recombinant), inactivated-zhzo*. FDA determined that the coagulation factor class is the scientifically valid pharmacologic class as supported by documented empiric evidence showing that ANDEXXA's structure, function, and mechanisms of action are those of a coagulation FXa variant. This pharmacologic class term is also clinically meaningful because it enhances the ability of professionals to understand physiologic effects related to the indication and to anticipate ANDEXXA's undesirable effects that may be associated with the pharmacologic class of coagulation factors -- bleeding because of the lack of action and thrombosis because of too much action.

10. LABELING

The proposed proprietary name for the product, ANDEXXA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and recommended to be acceptable on February 9, 2016. CBER communicated the acceptability of the proprietary name to the applicant on April 8, 2016. APLB reviewed the prescribing information, package, and container labels from a promotional and comprehension perspective and expressed concerns, which were resolved.

FDA comments and recommendations regarding the prescribing information and package and container labels were conveyed to Portola, and negotiated throughout the months of April and May 2018. A Boxed Warning was included in the prescribing

information to appropriately advise health care providers of the serious and life-threatening risks of ANDEXXA.

Final versions of the prescribing information and package and container labels submitted to the BLA on May 2, 2018 and April 25, 2018, respectively, were considered acceptable.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The CMC, toxicology, BIMO, facilities, statistical, and clinical pharmacology reviewers and inspectors did not identify any issues that would preclude approval of this BLA.

However, the clinical reviewers conclude that ANDEXXA's benefit/risk profile is unfavorable (see Risk/Benefit Assessment in Section 11b) and therefore do not recommend approval of this BLA.

The Director of the Office of Tissues and Advanced Therapies (OTAT) determined that, in the setting of a serious and life-threatening disorder with an unmet need for a product to reverse anticoagulation due to rivaroxaban or apixaban, the BLA includes sufficient evidence to support Accelerated Approval of ANDEXXA. Therefore, OTAT is approving ANDEXXA for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

An improvement in hemostasis has not been established. This approval is granted under the Accelerated Approval regulations (21 CFR 601 Subpart E), with a requirement for a postmarketing study to verify and describe ANDEXXA's clinical benefit. Continued approval for this indication may be contingent upon the results of postmarketing studies to demonstrate an improvement in hemostasis in patients.

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any factor Xa inhibitors other than apixaban and rivaroxaban.

b) Risk/ Benefit Assessment

This BLA is under consideration for Accelerated Approval, based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit (21 CFR 601.41). Members of the clinical review team agree that the BLA includes substantial evidence that ANDEXXA affects the surrogate endpoint of anti-FXa activity. However, the clinical review team has concerns that the BLA does not contain sufficient data to support that this surrogate is reasonably likely to predict a clinical benefit. Those concerns focus on the following: 1) ANDEXXA has a relatively short-duration (approximately 2 – 4 hours) effect on the surrogate; and 2) the available ANNEXA-4 study data do not show that ANDEXXA's effect on the surrogate correlated with clinical hemostasis in patients. These concerns regarding the surrogate endpoint are critical to the clinical review

team's recommendation against approval of this BLA. In addition to the concern that the surrogate endpoint is not reasonably likely to predict a clinical benefit, there are important safety concerns. Particularly, ANDEXXA is associated with serious and life-threatening events, including arterial and venous thromboembolic events, ischemic events including myocardial infarction and ischemic stroke, cardiac arrest, and sudden death. The clinical reviewers conclude that the uncertainty regarding the clinical benefit, in combination with concern about the safety of the product, results in an unfavorable overall benefit-risk profile of ANDEXXA.

However, the OTAT Office Director notes that there are reasons to believe that the effect on the surrogate is reasonably likely to predict a clinical benefit. First, there is strong biological plausibility that a decrease in anti-FXa activity, even if for only a few hours, could provide an opportunity for a clot to form that would result in hemostasis, with a resulting improvement in morbidity and mortality. In addition, the magnitude of ANDEXXA's effect on the surrogate was substantial, with a mean decrease in anti-FXa activity of greater than 90% in healthy volunteers who had received either rivaroxaban or apixaban. Therefore, the OTAT Office Director concludes that the observed decrease in anti-FXa activity is reasonably likely to predict a clinical benefit in morbidity and mortality in patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

The OTAT Office Director agrees with the clinical review team that ANDEXXA is associated with serious and life-threatening events, including arterial and venous thromboembolic events, ischemic events including myocardial infarction and ischemic stroke, cardiac arrest, and sudden death. However, the OTAT Office Director concludes that those risks are adequately mitigated by the ANDEXXA label, such that ANDEXXA's overall benefit-risk profile is favorable.

c) **Recommendation for Postmarketing Activities**

1. No safety issues have been identified that would warrant a Risk Evaluation and Mitigation Strategy (REMS).
2. Post-marketing Required Studies under Accelerated Approval

Study-18-513: "A Phase 4 randomized trial of ANDEXXA in acute intracranial hemorrhage in patients receiving oral factor Xa inhibitors"

This open-label, randomized trial will include at least 440 adult patients who developed acute intracranial hemorrhage following the treatment with rivaroxaban, apixaban, or edoxaban 15 hours or less prior to randomization. The enrolled patients will be administered ANDEXXA (high or low dose) or standard of care other than ANDEXXA according to 1:1 randomization scheme. To describe and verify the hemostatic effect of ANDEXXA, patients will be assessed with the National Institute of Health Stroke Scale and computed tomography or magnetic resonance imaging at 12-hours post-randomization. The trial assessments will also include evaluation of occurrence of the safety events of special interest, including but not limited to:

stroke, transient ischemic event, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, arterial systemic embolism, sudden death, and events suspicious for thrombosis, embolism, and ischemia—all to be observed at least 3 days for immediate occurrence and at least 30 days with weekly intervals for delayed occurrence. The assessments of the hemostatic effect will be made by an adjudication committee blinded to the treatment allocation.

The following milestones are provided:

- Submission of the Study Protocol: April 17, 2018
 - Study Completion Date: October 31, 2022
 - Date of Final Study Report Submission: April 30, 2023
3. The Office of Biostatistics and Epidemiology (OBE) will request an updated pharmacovigilance plan which includes identification of potential risks and missing information, and acknowledges as an important identified risk thromboembolic events as well as any other newly identified and potential safety concerns. The applicant's plans for routine pharmacovigilance monitoring will include submission of all serious, unexpected (unlabeled) adverse event reports to FDA within 15 days and quarterly submission of Periodic Adverse Experience Reports for the first 3 years after licensure. Routine surveillance also includes continuous monitoring of the safety profile including signal detection, issue evaluation, labeling as necessary and liaison with regulatory authorities.