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<tr><td>Application Type</td><td>Original Application</td></tr>
<tr><td>STN</td><td>125586/0</td></tr>
<tr><td>CBER Received Date</td><td>December 18, 2015</td></tr>
<tr><td>PDUFA Goal Date</td><td>August 17, 2016</td></tr>
<tr><td>Division / Office</td><td>DHRR /OBRR</td></tr>
<tr><td>Priority Review</td><td>Yes</td></tr>
<tr><td>Reviewer Name(s)</td><td>Lisa M. Faulcon, MD</td></tr>
<tr><td>Review Completion Date / Stamped Date</td><td></td></tr>
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<tr><td>Applicant</td><td>Portola Pharmaceuticals</td></tr>
<tr><td>Established Name</td><td>Coagulation Factor Xa (Recombinant), Inactivated</td></tr>
<tr><td>(Proposed) Trade Name</td><td>ANDEXXA</td></tr>
<tr><td>Pharmacologic Class</td><td></td></tr>
<tr><td>Formulation(s), including Adjuvants, etc.</td><td>Intravenous injection</td></tr>
<tr><td>Dosage Form(s) and Route(s) of Administration</td><td>Lyophilized powder with nominal dose of 100 mg in a single-use vial</td></tr>
<tr><td>Dosing Regimen</td><td>
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<tr><th>Dose</th><th>Initial IV Bolus</th><th>Follow-On IV Infusion</th></tr>
<tr><td>Low Dose</td><td>400 mg at a target rate of 30 mg/min</td><td>4 mg/min for up to 120 minutes</td></tr>
<tr><td>High Dose</td><td>800 mg at a target rate of 30 mg/min</td><td>8 mg/min for up to 120 minutes</td></tr>
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<tr><td>Proposed Indication(s) and Intended Population(s)</td><td>For patients treated with a direct or indirect Factor Xa inhibitor when reversal of anticoagulation is needed in situations such as:
• In life-threatening or uncontrolled bleeding
• (b) (4)</td></tr>
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GLOSSARY

(b) (4)	
ADA	anti-drug antibodies
AE	adverse event
(b) (4)	
BDS	bulk drug substance
BLA	biologics license application
BPM	beats per minute
CDER	Center for Drug Evaluation and Research
CHO	chinese hamster ovary
CRF	case report form
DP	drug product
DSMB	data safety monitoring board
DVT	deep vein thrombosis
EAC	Endpoint Adjudication Committee
EAP	Efficacy Analysis Population
ECG	electrocardiogram
ED	emergency department
ETP	endogenous thrombin potential
GI	gastrointestinal
HCT	historical controlled trial
ICH	intracranial hemorrhage
IND	investigational new drug
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
mRS	modified Rankin score
NVAF	nonvalvular atrial fibrillation
PCC	prothrombin complex concentrate
PD	pharmacodynamics
PE	pulmonary embolism
PK	pharmacokinetic
PP	per-protocol population
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SD	study day
SDH	subdural hematoma
SGE	special government employee
TAT	thrombin-antithrombin
TFPI	tissue factor pathway inhibitor
ULN	upper limit of normal
VKA	vitamin-K antagonist
VTE	venous thromboembolism

1. Executive Summary

Portola submitted a Biologics License Application (BLA) for Coagulation Factor Xa (Recombinant), Inactivated for the following proposed indications:

For patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed in situations such as:

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

The proprietary name is Andexxa and the International Nonproprietary Name is andexanet alfa. The active ingredient of ANDEXXA is a genetically modified variant of human Coagulation Factor Xa (FXa) produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line. Andexxa is available in lyophilized form for intravenous administration after reconstitution with sterile Water for Injection. There are two dosing regimens. Recommended dosage is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor:

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

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 Xa inhibitors in patients experiencing a serious uncontrolled bleeding event (b) (4) " on February 23, 2015.

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 (Module 1, Module 2, Module 3 and Module 5), were received on December 17, 2015, which started the review clock. The current action date for this BLA is August 17, 2016. This application is being 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."

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 35 subjects experiencing acute major bleed who received Andexxa for reversal (target population) in the ongoing confirmatory study. Of the 282 subjects who received Andexxa, 247 (87.6%) were healthy volunteer subjects and 35 (12.4%) were in the target population. A total of 24 subjects received the lyophilized product at

the proposed licensed low dose of 400 mg bolus followed by a 120 min infusion at 4 mg/min and 32 received the high dose of 800 mg bolus followed by a 120 min infusion at 8 mg/min. An additional 6 subjects received a 420 mg bolus dose followed by a 120 min infusion at 4 mg/min, which was the dosing regimen for the liquid formulation of the product. The clinical development program is summarized in table 6 of section 5.3. All studies were performed under IND 15089; phase 3 studies were reviewed under the breakthrough therapy designation program.

In the clinical development program for Andexxa, clinical Trials 14-503 and 14-504 provided the primary evidence to support safety and efficacy of the product. Data from the ongoing confirmatory study (14-505) were submitted as supportive evidence of safety and effectiveness.

Phase 3 Studies in Healthy Volunteers
Trials 14-503 and 14-504 were conducted as randomized, double-blind, placebo-controlled trials to demonstrate the ability of Andexxa to reverse anticoagulation of apixaban (Trial 14-503) or rivaroxaban (14-504) and evaluate 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 min 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 min infusion at 8 mg/min. The primary objective of both studies was to compare Andexxa 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. For the primary efficacy analysis, a comparison of primary endpoints between the two treatment groups was conducted using an exact Wilcoxon rank-sum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level; study success was claimed if statistically significant differences in anti-FXa activity reduction between the two groups were observed.

Secondary endpoints included:

- The occurrence of ≥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 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.
- The change in thrombin generation and the occurrence of thrombin generation above the lower limit

Subjects were domiciled at the study site for 8 days, and subsequently followed for safety through Day 43. Subjects remained on study for approximately 8 to 12 weeks, depending on the length of screening. The study periods were as follows:
• Screening: Days -42 to -1
• Anticoagulant Dosing: Days 1 to 4
• Andexxa/placebo Dosing: Day 4
• Safety Follow-Up: Days 5 to 43 (+3)

Study Population and Disposition
In study 14-503, 68 subjects were enrolled and received apixaban (34 in Part 1 and 34 in Part 2). Of these, 66 subjects were randomized (34 subjects in Part 1 [25 Andexxa, 9 placebo] and 32 in Part 2 [24 Andexxa, 8 placebo]). Of the 65 subjects included in the safety database, most were male (41/65; 63%), white (62/65; 95%), and not Hispanic or Latino (38/65; 58%). The mean (SD) age in Part 1 was 60.4 (5.8) years (median of 59 years with a range of 50 to 73); for Part 2 the mean age was 59.4 (7.5) years (median of 56.5 years with a range of 50 to 73).

In part 1, 33 of the 34 randomized subjects completed the study. One subject ((b) (6)) randomized to the Andexxa group did not receive study drug. In part 2, all 32 randomized subjects completed the study. 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.

In study 14-504, 80 subjects were enrolled and received rivaroxaban (41 in Part 1 and 39 in Part 2). All 80 subjects were randomized (41 subjects in Part 1 [27 Andexxa, 14 placebo] and 39 in Part 2 [26 Andexxa, 13 placebo]). Of the 80 subjects included in the safety database, most were male (48/80; 60%), white (60/80; 75%), and not Hispanic or Latino (53/80; 66%). The mean (SD) age in Part 1 was 55.2 (3.8) years (median of 55 years with a range of 50 to 65); for Part 2 the mean age was 57.3 (5.16) years (median of 57 years with a range of 50 to 68).

In part 1, all 41 randomized subjects completed the study. 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 Confirmatory Study
As a confirmatory study, Portola is conducting a multicenter, prospective, open-label, one armed study of Andexxa in approximately 250 subjects (162 evaluable) presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin.

Patients are primarily enrolled in the emergency department (ED) upon presentation with an acute major bleeding episode; however, patients who experience an acute major bleeding episode while hospitalized in various inpatient units may also be enrolled. The primary objectives are to:

- Demonstrate the decrease in anti-FXa activity following Andexxa treatment. The study will be considered to have met the first primary efficacy objective if there is a statistically significant ($p<0.05$) percent decrease in anti-FXa activity from the pre-treatment baseline to the evaluation period nadir (where the evaluation period starts 5 minutes following the end of the Andexxa bolus and ends just prior to the end of the Andexxa infusion).
- Evaluate the hemostatic efficacy of Andexxa in patients receiving FXa inhibitors who have acute major bleeding and reduced FXa activity. The study will be considered to have met the second primary efficacy objective if the proportion of patients with excellent or good hemostasis (as adjudicated by the independent Endpoint Adjudication Committee [EAC]) is statistically significantly higher than 50% ($p<0.05$).

Secondary Objectives include:

- To assess the relationship between decrease in anti-FXa activity and the achievement of hemostatic efficacy in patients receiving FXa inhibitors who have acute major bleeding and reduced FXa activity.
- To evaluate the overall safety of Andexxa, including adjudicated TEs and antibodies to FX, FXa, and Andexxa.
- To evaluate the 30-day all-cause mortality.

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. 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 hemorrhage (ICH); and transfusion-corrected hemoglobin and hematocrit for non-visible bleeding. Hemostatic efficacy is adjudicated by an independent Endpoint Adjudication Committee (EAC) using a three-point rating scale (Appendix III) 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 two primary hierarchical endpoints being evaluated are:

1. The percent change from baseline in anti-FXa activity to the nadir from the evaluation period (where the evaluation period starts 5 minutes following the end of the Andexxa bolus and ends just prior to the end of the Andexxa infusion)
2. The achievement of hemostatic efficacy of stopping an ongoing major bleed at 12 hours from the end of the Andexxa infusion.

The study duration for any individual patient will be up to 37 days:
• Screening Period: <1 day (Day 1)
• Treatment Period: <1 day (Day 1)

• Safety Evaluation Period: 3 days (Days 1–3)
• Extended Safety Follow-Up Period (related AEs, survival): ~26 days (Day 4 to the Day 30 study visit)

Note: FDA did not agree with the uncontrolled design of this study and requested that Portola conduct a usual care cohort study to serve as the control population.

Study Population and Disposition
As of March 11, 2016, 77 (out of 250 planned) subjects have been enrolled and treated with Andexxa, of which 35 had information available for the evaluation of efficacy. Of the 35 subjects with available information, 18 (51%) were males and 17 (49%) were females with a mean age of 77.6 years (median: 81 years with a range of 55 to 95). A total of 13 subjects presented with major bleeds while on rivaroxaban, 18 on apixaban, and 4 on enoxaparin. The majority of bleeding events were ICH (n=13) and gastrointestinal (GI; n=16). The remaining were retroperitoneal (n=3), visible (n=1), pericardial (n=1), and intra-articular (n=1).

A total of 22/35 (63%) of evaluable subjects had moderate impaired renal function (eGFR <60 mL/min/1.73 m^2). Of these, 4 subjects had baseline anti-FXa levels that were greater than 2 standard deviations from the mean anti-FXa activity levels observed in healthy volunteer studies.

Of the 35 subjects with available information, 2 subjects ((b) (6) and (b) (6)) had bleeds that were not considered major bleeds and adjudication of efficacy for one subject ((b) (6)) is pending. An additional subject ((b) (6)) had undetectable anti-FXa levels at baseline (<4 ng/mL), suggesting that the bleed was not from anticoagulation. These subjects were excluded from the analysis. In addition, two subjects ((b) (6) and (b) (6)) had bleeds that were considered not evaluable by the EAC.

Saftey data for an additional 22 subjects were submitted in the 180-day Safety Update. No subjects have been discontinued.

Efficacy Results

Phase 3 Studies in Healthy Volunteers

The primary efficacy analysis compared the primary endpoint of percent change from baseline in anti-FXa activity at the nadir between the two treatment groups using an exact Wilcoxon ranksum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level. The primary efficacy analyses for Part 1 and Part 2 were done using the Efficacy Analysis (mITT) Population, which was comprised of subjects who received any amount of study drug and had baseline values for anti-FXa and ≥1 of the following time points: +2 minute or +5 minute time point after the end of the bolus or 110-minute time point during the continuous infusion, -2 minute time point during the continuous infusion, or +5 minute time point after the end of the continuous infusion.

Both studies won on all primary and secondary efficacy endpoints: statistically 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.

Apixaban

In Part 1, the mean (SD) anti-FXa activity levels after anticoagulation with apixaban (baseline) were 211.3 ng/mL (62) and 197.6 ng/mL (63.2) for the Andexxa and control groups, respectively. Nadir levels (SD) of anti-FXa were lowest two minutes after the bolus infusion at 12.5 ng/mL (3.4). The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -93.9% (1.6%) for the Andexxa group and -20.7% (8.6%) for the placebo group ($p<0.0001$). Anti-FXa returned to levels observed in the placebo group (or higher) within 180 minutes after the end of the bolus. Mean unbound levels of apixaban decreased significantly from baseline levels of 11.1 ng/mL (3.3) to a nadir of 1.8 ng/mL (0.6) and returned to levels observed in the placebo group (or higher) within 120 minutes after the end of the bolus. This decrease was significantly higher in subjects who received Andexxa than in subjects who received placebo ($p<0.01$).

In Part 2, the mean (SD) anti-FXa activity levels after anticoagulation with apixaban were 173 ng/mL (50.5) and 191.7 ng/mL (34.3) for the Andexxa and control groups, respectively. Nadir levels of anti-FXa were lowest two minutes after the bolus infusion at 10.9 ng/mL (2.3). The mean percent change from baseline in anti-fXa activity at the nadir was -92.3% (±2.8%) for the Andexxa group and -32.7% (±5.6%) for the placebo group ($p<0.0001$). Anti-FXa returned to levels observed in the placebo group within 300 minutes after the end of the bolus plus infusion. Mean unbound levels of apixaban decreased significantly from baseline levels of 7.9 ng/mL (2.8) to a nadir of 1.4 ng/mL (0.4) and returned to levels observed in the placebo group within 240 minutes after the end of the bolus. This decrease was significantly higher in subjects who received Andexxa than in subjects who received placebo ($p<0.01$).

For both parts, all subjects in the Andexxa group had ≥80% reduction in anti-FXa activity.

Endogenous thrombin potential (ETP) from baseline to its peak increased significantly more in subjects who received Andexxa than in subjects who received placebo ($p<0.0001$), in both Part 1 and Part 2.

Rivaroxaban

In Part 1, the mean (SD) anti-FXa activity levels after anticoagulation with rivaroxaban (baseline) were 318.2 ng/mL (75) and 253.6 ng/mL (60.7) for the Andexxa and control groups, respectively. Nadir levels (SD) of anti-FXa were lowest two minutes after the bolus infusion at 28.2 ng/mL (52.2). Anti-FXa returned to levels observed in the placebo group within 120 minutes after the end of the bolus.The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -92.2% (10.7%) for the Andexxa group and -18.4% (14.7%) for the placebo group ($p<0.0001$; $n=13$). Mean unbound levels of rivaroxaban decreased significantly from baseline levels of 27.3 ng/mL (6.5) to a nadir of

4 ng/mL (3.9) and returned to levels observed in the placebo group within 120 minutes after the end of the bolus.

In Part 2, the mean (SD) anti-FXa activity levels after anticoagulation with rivaroxaban were 335.3 ng/mL (91) and 317.2 ng/mL (91) for the Andexxa and control groups, respectively. The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -96.7% (1.8%) for the Andexxa group and -44.7% (11.7%) for the placebo group ($p<0.0001$). All subjects in the Andexxa group had ≥80% reduction in anti-FXa activity. Nadir levels of anti-FXa were lowest 110 minutes after the bolus infusion at 10.9 ng/mL (6), as compared to levels of 16.8 ng/mL (10.3) at two minutes. Anti-FXa returned to levels observed in the placebo group within 120 minutes after the end of the bolus plus infusion (Figure 4).

All but one subject treated with Andexxa had ≥80% reduction in anti-FXa activity, as compared to no subjects in the placebo group. Per the applicant, subject (b) (6) was enrolled in Part 1, 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 ($p<0.0001$), in both Part 1 and Part 2.

Phase 3b/4 Confirmatory Study

Hemostatic Efficacy

Overall, per the applicant, 27/35 (77%) of subjects achieved excellent/good hemostatic efficacy; however, this analysis included subjects that did not have a major bleed (n=2), had a pending efficacy rating (n=1), or had detectable anti-FXa levels of ≥4 ng/mL (n=1). Exclusion of these subjects resulted in similar efficacy of 24/31 (77%). Two subjects had unevaluable bleeds and 5 were assessed as 'poor/none by the EAC. Narratives for the 5 subjects with efficacy assessments of 'poor/none' are provided below:

- Subject (b) (6) was a 90 year-old white male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with a SDH due to blunt trauma. The subject was assigned to low dose Andexxa. Anti-FXa levels were reduced by 83% following the Andexxa infusion (baseline anti-FXa was 176.1 ng/mL). The 1-hour post-infusion CT showed a significant increase in thickness from 12.23 mm at baseline to 21 mm. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Poor/none.' The subject was discharged from the hospital on SD 3 and re-anticoagulated with rivaroxaban, 20 mg once daily.
- Subject (b) (6) was an 84 year-old, white female taking apixaban 2.5 mg bid for atrial fibrillation who presented to the ED with a CT-confirmed intraparenchymal bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 95% following the Andexxa

infusion (baseline anti-FXa was 117.7 ng/mL). The subject had an interim development of intraventricular hemorrhage noted after the 1 hr post-infusion assessment that was not documented at baseline.

- Subject (b) (6) was an 86 year-old male taking apixaban 2.5 mg twice daily for atrial fibrillation and portal venous thrombosis who presented to the ED with a GI bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. The EAC commented that there was a significant decrease in the corrected hematocrit and hemoglobin, despite multiple blood transfusions. An EGD and colonoscopy were unrevealing. Anti-FXa levels were reduced by 94% following the Andexxa infusion (baseline anti-FXa was 147.3 ng/mL).
- Subject (b) (6) was a 78 year-old white female taking rivaroxaban 15 mg once daily for atrial fibrillation, who presented to the ED with a retroperitoneal bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 87% following the Andexxa infusion (baseline anti-FXa was 389.1 ng/mL). The adjudication committee noted that bleed was reported as retroperitoneal, however, assessed as muscular/skeletal (M/S). This bleed should have been assessed as other-non-visible bleeding with the CT scans or images used for assessment. The site had not repeated the CT scan at the 12-hour assessment, so there were no comparisons for the size of the bleed. Per the applicant, the source documents and CRFs showed that the pain stayed the same up to the 12-hour assessment, and hemoglobin had fallen after the infusion. Therefore, the final post-treatment hemostatic efficacy assessment by the adjudication committee is poor/none.
- Subject (b) (6) was a 90 year-old white male taking apixaban 2.5 mg, twice daily for atrial fibrillation, who presented at the ED with an ICH noted specifically to include a subarachnoid hemorrhage, and separately a nonvisible bleed (respiratory tract - pleural). The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 89% following the Andexxa infusion (baseline anti-FXa was 65.2 ng/mL). The intracranial bleeding continued to expand -8.26 mL (9 hours pre-bolus), 12.30 mL (right before bolus), 63.90 mL (4 hours postinfusion), 42.06 mL (12 hours post-infusion).

For apixaban, 18 subjects had available information for evaluation by the EAC. A total of 15 subjects were considered major bleeds, had detectable anti-FXa activity levels at baseline and an efficacy rating by the EAC, including 1 that was treated for a retroperitoneal bleed, 1 for a visible bleed, 1 for intra-articular bleed, 5 for GI bleeds, and 7 with ICH. All subjects received the low dose Andexxa regimen (400 mg bolus + 480 mg infusion). A total of 10/15 (67%) of subjects achieved excellent/good hemostatic efficacy; 3 (19%) bleeds received ‘poor/none’ ratings by the EAC; and 2 bleeds were not evaluable.

For rivaroxaban, 12 out of 13 subjects with available information were considered to have major bleeds, including 1 that was retroperitoneal, 7 that were GI, and 4 that were ICH bleeds. Two subjects received the high dose Andexxa regimen (800 mg bolus + 960 mg infusion) and the other subjects received the low dose. A total of 10/12 (83%) of

subjects achieved excellent/good hemostatic efficacy; 2 bleeds received 'poor/none' ratings by the EAC.

For enoxaparin, all 4 subjects achieved excellent/good hemostatic efficacy. These data were judged insufficient to support a labeled claim of reversal of anticoagulation for this drug.

Percentage Change From Baseline in Anti-FXa Activity to the Nadir
Note: as a conservation approach, anti-FXa levels reported as <4 ng/mL were assigned a numerical value of 4 ng/mL, rather than zero.

Apixaban
The mean baseline anti-FXa activity level for the 15 subjects with major bleeds and detectable anti-FXa activity levels was 222.3 ng/mL (median 147.3 ng/mL; range: 49.1 to >950 ng/mL). For the 14 subjects with available data, the mean percent change from baseline anti-FXa activity to post-bolus was -79% (median -92%; range -23 to -97%). For the 13 subjects with available data, the mean percent change from baseline anti-FXa activity to post-infusion was -79% (median -92%; range -42 to -95%). *Note: although 16 subjects were considered to have had a major bleed, subject* (b) (6) *had a baseline level of <4 ng/mL suggesting that the cause of the bleed was not directly related to anticoagulation and therefore was excluded from the analysis by this reviewer.*

The mean anti-FXa activity at four hours post-infusion was 180.2 ng/mL. Mean post-infusion levels at 8 and 12 hours were 165.1 and 129.7 ng/mL, respectively. Mean anti-FXa levels at 4, 8, and 12 hours post bolus and continuous infusion were considered to be in the range of therapeutic anticoagulation. Anti-FXa activity levels were not obtained after the 12 hour time-point.

Three subjects had baseline anti-FXa activity levels that were ≥2 SD above the mean from the phase 3, part 2 healthy volunteer study: [subjects (b) (6) (retroperitoneal/skin bleed; anti-FXa activity level: 498 ng/mL), (b) (6) (GI; 487.1 ng/mL) and (b) (6) (GI; >950 ng/mL)]. For all three subjects with higher baseline values, the percent reduction after the infusion was <50%. *Note: percent reduction for subject* (b) (6) *and* (b) (6) *was higher after the bolus (68% and 78%) but anti-FXa levels increased during the infusion, resulting in a lower percent reduction after the infusion.*

Exclusion of the data from subjects with baseline levels that were ≥2 SD resulted in a mean percent change in anti-FXa activity of -92.4%.

Rivaroxaban
The mean baseline anti-FXa activity level for the 12 subjects was 276.9 ng/mL (SD: 61 ng/mL; median 200.4 ng/mL; range: 134.7 to 862.4 ng/mL). The mean percent change from baseline anti-FXa activity to post bolus was -81% (median -92%, range -22 to -98%). The mean percent change from baseline anti-FXa activity to post infusion was -79% (median -86.5%, range -42 to -98%).

For the 10 subjects with available data, the mean anti-FXa activity at four hours post-infusion was 173.1 ng/mL. Mean post-infusion levels at 8 and 12 hours were 141.1 and 109.8 ng/mL, respectively. Mean anti-FXa levels at 4, 8, and 12 hours post bolus and continuous infusion were considered to be in the range of therapeutic anticoagulation. Anti-FXa activity levels were not obtained after the 12 hour time-point.

Mean unbound levels of rivaroxaban decreased from baseline levels of 21.1 ng/mL to 6.6 ng/mL post-infusion (median 18.1, range: 10.4 to 48.5). Mean levels at 4, 8, and 12 hours were 15, 9.7 and 5.2, respectively.

One subject had baseline anti-FXa activity levels that were ≥2 SD above the mean from the phase 3, part 2 study: subject (b) (6) (GI bleed) had an anti-FXa activity level of 862 ng/mL at baseline; treatment with Andexxa resulted in 44% of anti-FXa activity. Hemostatic efficacy was adjudicated as excellent, despite nadir anti-FXa activity levels that remained within the therapeutically anticoagulated range following administration of Andexxa.

Two subjects out of the 10 subjects treated with the low dose had lower-than-expected decreases in mean percent changes in anti-FXa activity, despite having levels within the expected therapeutic range:

- Subject (b) (6) was a 67 year-old male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with bright red blood per rectum, which started 2 hours and 25 minutes after the last dose of rivaroxaban. He received the low dose of Andexxa (time from last dose of anticoagulant to Andexxa was 9 hours and 40 minutes). Mean percent changes post-bolus and post-infusion were:

Anti-FXa activity (baseline)	**Anti-FXa after bolus**	**Percent reduction**	**Anti-FXa after infusion**	**Percent reduction**
227.8	178.5	22	132.8	42

- Subject (b) (6) was a 77 year-old African-American female taking rivaroxaban 20 mg once daily for venous thromboembolism prevention who presented to the ED with a GI bleed 11 hours after the last dose of rivaroxaban. She received the low dose of Andexxa (time from last dose of anticoagulant to Andexxa was 18 hours and 20 minutes). Mean percent changes post-bolus and post-infusion were:

Anti-FXa activity (baseline)	**Anti-FXa after bolus**	**Percent reduction**	**Anti-FXa after infusion**	**Percent reduction**
295.2	6.3	98	136.5	54

Enoxaparin
Four subjects with acute major bleeding while on enoxaparin were treated with Andexxa, including 2 subjects with GI bleeding, 1 subject with a retroperitoneal bleed, and 1 subject with pericardial bleeding. Three subjects received high dose Andexxa. The mean baseline anti-FXa activity level for these 4 subjects was 0.42 ng/mL (median 0.46 ng/mL; range: 0.13 to 0.61 ng/mL). For the 3 subjects with available data, the mean percent

change from baseline anti-FXa activity to post infusion was -51%. These data were insufficient to support a labeled claim of reversal of anticoagulation for this drug.

Subpopulations
GI bleeds
Sixteen subjects with GI bleeds were enrolled: 6 subjects on apixaban, 8 subjects on rivaroxaban and 2 subjects on enoxaparin. Subject (b) (6) (apixaban) was excluded by this reviewer because the baseline anti-FXa activity level was <4 ng/mL and subject (b) (6) (rivaroxaban) had a bleed that was not considered major.

For the 12 remaining subjects treated with apixaban or rivaroxaban, the mean baseline anti-FXa activity levels were 337 ng/mL. Treatment with Andexxa resulted in 81% reduction in anti-FXa activity levels post-bolus and 71% reduction post-infusion. Based on the EAC's adjudication, a total of 11/12 (92%) received a rating of excellent/good and 1 (subject (b) (6)) received poor/none.

However, as noted previously, FDA was unable to confirm these successful adjudications because this reviewer determined that at least 2 subjects did not meet the eligibility criteria of having an acute major or life-threatening GI bleed, adjudication assessments were inconsistent with clinical findings for an additional 2 subjects, and bleeding appeared to have been resolved prior to Andexxa treatment for an additional 3 subjects.

Because of the dosing concerns and limited duration of effect, as evidenced by the return of anti-FXa activity to >50% of baseline values by the 4-hour assessment time-point, a subgroup analysis was done to evaluate hemostatic efficacy for subjects with ICH where clinical guidelines recommend reversal of anticoagulation for at least 24 hours.

Thirteen subjects with ICH were enrolled, of which 12 were considered to have a major bleed and 11 had available efficacy ratings. An additional subject ((b) (6)) was excluded because this subject received two platelet transfusions within 3 hours of completing the Andexxa infusion; the platelet contribution to the hemostatic process confounds the assessment of efficacy in this case. Data from subject(s) with CT assessments done more than 2 hours after the pre-specified 12-hour scheduled efficacy assessment were excluded from the analysis, resulting in exclusion of data from an additional subject ((b) (6)).

For the 9 remaining subjects, mean baseline anti-FXa activity levels were 168.8 ng/mL. Treatment with Andexxa resulted in 94% reduction in levels post-bolus and 91% reduction post-infusion. A total of 6/9 (67%) received a rating of excellent/good and 3 received poor/none.

Efficacy Conclusions: These results show that treatment with Andexxa results in a rapid reversal of anticoagulation that persists for the duration of the infusion; however depth of reversal is not sustained once the infusion is complete. The apparent rebound that is observed at the end of the infusion suggests that a longer infusion or repeat dosing may be required to maintain a sustained reversal of anti-

FXa activity levels. Furthermore, a prolonged PD effect in patients with moderate and severe renal insufficiency may be required because the rate of elimination of some direct FXa inhibitors is known to be slower in renally impaired subjects; this could likely be achieved by longer infusions, the safety of which has not been evaluated.The submitted data from the ongoing confirmatory study is insufficient to allow for meaningful conclusions to be drawn about efficacy in the bleeding population, in terms of correlation between the decrease in anti-FXa activity and achievement of hemostatic efficacy. Adjudication of hemostatic efficacy as successful (i.e. rating of excellent or good) despite nadir anti-FXa activity that remained within the therapeutic (anticoagulated) range following andexanet administration questions the adequacy of anti-FXa activity as a surrogate marker likely to predict clinical outcomes. Preliminary data show that the depth of reversal is not as robust in patients presenting with supratherapeutic anti-FXa levels, which could result in continued bleeding or evidence of re-bleeding. The applicant was asked to identify and justify a target anti-FXa level that would be associated with an acceptable risk of bleeding; however the data to support the 30 ng/mL level proposed were judged insufficient. To date, no subject in this trial had reported re-bleeding; however, the database may not be large enough to capture these events, particularly if the incidence of re-bleeding is low. The fact that 20% of subjects on rivaroxaban who were dosed with the low dose of Andexxa had low response rates (22% of those dosed within therapeutic range), combined with the more consistent results achieved with the higher dose in phase 3 healthy volunteer studies, suggest that the higher dose may be more effective; this conclusion is also supported by data from phase 2 studies demonstrating a dose-dependent relationship with nadir levels of unbound rivaroxaban. Results from preliminary data from the ongoing confirmatory study in patients being treated with FXa inhibitors and experiencing life-threatening bleeding may be consistent with clinical benefit in that, based on EAC adjudication, 24/31 (77%) received excellent or good efficacy ratings. However, because FDA was not able to confirm the adjudication ratings and because control rates of success are unknown, the clinical significance of these findings are questionable.

Although the applicant proposed an indication for reversal of direct or indirect FXa inhibitors, there were insufficient data to support an indication for indirect FXa inhibitors (e.g., enoxaparin) or edoxaban as reversal of these drugs was not adequately studied in phase 3 studies. In addition, there were no data submitted to support the use of this product in (b) (4) .

Safety Results

The labeled safety concerns for Andexxa are: hypersensitivity/anaphylactic reactions, thromboembolic events, development of inhibitors and antibodies against CHO (b) (4) . The safety of Andexxa was assessed using the following endpoints: frequency of adverse events, vital signs, clinical laboratory tests, and immunogenicity testing. Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities, and were analyzed based on the principle of treatment emergence during study treatment. All safety analyses were based on the safety population, which

included all subjects who received at least one dose of Andexxa or placebo. In each clinical study, samples from subjects treated with either Andexxa or placebo were tested for the presence of antibodies against Andexxa, FX, and FXa.

Of the 349 heathy volunteers studied, 247 were dosed with Andexxa and 102 received placebo. A total of 317 subjects were anticoagulated with a direct or indirect FXa inhibitor and were included in the integrated summary of safety, including 223 that received Andexxa and 94 that received placebo. An additional 57 subjects with major bleeding events received Andexxa.

A total of 8 deaths occurred in the confirmatory study, including one that was considered related to Andexxa (see section 8.4.1). No healthy volunteer subjects died while on study.

Of the 223 healthy volunteers subjects dosed, 5 (2.2%) were discontinued due to loss to follow-up (n=4) or subject withdrawal (n=1). One subject in the placebo group had an adverse event and was withdrawn from the study. The number of subjects who were withdrawn and the reasons for their withdrawal did not undermine the data or the conclusions drawn about the clinical trial.

Overall, the incidence of TEAEs was similar between the pooled Andexxa and pooled placebo analysis sets for any TEAE (53.2% vs. 59.3%) and TEAEs within the first hour of study drug administration (22.0% vs. 18.6%). No new safety signals were identified. TEAEs related to study drug were higher in the Andexxa group (26.3% vs. 18.6%). The most common TEAE in the pooled Andexxa that was greater than placebo was infusion-related reaction (17.5% vs. 6.4%, respectively). The other most common AEs were either reported at similar rates between Andexxa and placebo (headache [7.6% vs. 7.4%, respectively]), or were more common in placebo subjects (dermatitis contact [2.2% vs. 7.4%], vessel puncture site pain [1.8% vs. 6.4%], respectively). According to the applicant, the most common TEAEs related to study drug in the pooled Andexxa and pooled placebo analysis sets were infusion-related reaction (17.5% vs. 6.4%, respectively), and dizziness postural (1.3% vs. 3.2%, respectively).

A total of 20 subjects had serious adverse events (SAEs) during clinical trials of Andexxa including 1 report of bilateral pneumonia and 1 report of a chemical pregnancy in study 11-501. Of the 57 patients in the safety population of the confirmatory study, 37 SAEs were reported in 18 subjects, included one that was considered related to the product.

There were 102 infusion-related AEs in 39 subjects in the Andexxa group and 14 events in 4 subjects in the placebo group. Most infusion-related reaction AEs were mild in severity. Three subjects enrolled in study 12-502 had 8 moderate or severe infusion-related reactions that occurred within the first hour of infusion. All infusion-related reactions were considered by the Investigator and this clinical reviewer as related to study drug and resolved. The infusion-related reaction symptoms that occurred in ≥ 3 subjects were flushing (17 Andexxa), feeling hot (7 Andexxa, 1 placebo), cough (7 Andexxa), dysguesia (6 Andexxa, 1 placebo), dyspnea (6 Andexxa), chest discomfort (5 Andexxa, 1 placebo), palpitations, abdominal discomfort, urticaria, pruritus, and peripheral coldness,

(3 Andexxa), and ocular hyperaemia (2 Andexxa, 1 placebo). No subjects in the Phase 3b/4 study (14-505) had an infusion reaction.

Elevations of D-dimer, and of prothrombin fragment 1+2 were higher in the pooled Andexxa analysis set than the pooled placebo analysis set. These elevations were not associated with clinical evidence of thrombosis in healthy volunteer subjects. In addition, Andexxa completely inhibited Tissue Factor Pathway Inhibitor (TFPI) activity approximately 3 hours after Andexxa bolus administration and returned to 25% of the pre-treatment level at 24 hours. TFPI activity was not investigated in phase 3 studies in the presence of FXa inhibitors; however, TFPI antigen was reduced to a similar degree following Andexxa in both phase 1 and 3 studies.

Nine subjects in the confirmatory study had 16 AEs that were considered "potentially thrombotic in nature." The events occurred 2 to 30 days after dosing in subjects with medical histories of recent DVT alone (2 subjects), DVT and atrial fibrillation (2 subjects), or atrial fibrillation alone (5 subjects). None of the subjects were re-anticoagulated after treatment with Andexxa. Two of the thrombotic events (ischemic stroke on study day (SD) 2 in one subject and multiple DVTs on SD 3 in another) were considered related to Andexxa by this reviewer.

The initial (b) (4) formulation had a rate of confirmed low titer non-neutralizing antibodies against Andexxa (2%) while the rate observed for the lyophilized formulation was higher (20%). The overall rate of confirmed anti-Andexxa antibodies was 12.1% in all healthy subjects during the clinical development phase of Andexxa. Portola has not developed assays to detect anti-drug antibodies that may neutralize endogenous coagulation factors X and Xa; therefore no conclusions can be drawn about the risk of development of neutralizing antibodies (inhibitors). The development of a neutralizing antibody in a patient treated with Andexxa would significantly alter the risk-benefit profile of the drug.

The levels of sucrose in the highest single dose of Andexxa administered in the Phase 3 and ANNEXA 4 studies are within FDA's accepted range for product specifications and as expected, no healthy volunteer subjects developed evidence of sucrose-related acute kidney injury; however, creatinine levels were not adequately assessed in the confirmatory study so similar conclusions cannot be made regarding bleeding patients with or without baseline renal insufficiency.

Summary Conclusions: Generalizability of the healthy volunteer studies to the target population is limited because renally impaired patients were excluded, as were patients with an increased baseline risk of thrombosis. The bleeding/re-bleeding risk and incidence of thrombosis may be different in these patients and therefore clinical outcomes may be different. Thrombotic events were an expected AE as Andexxa has some procoagulant properties and because effectively reversing anticoagulation in patients who have an increased baseline risk for thrombosis increases the likelihood that such an event will occur; however, the lack of a control group makes it difficult to understand the clinical significance of these findings.

Furthermore, the inadequacy of the evaluation of Andexxa's procoagulant properties, sucrose-related renal toxicity, and immunogenicity makes it difficult to better characterize the safety of this product in the target population. Before approval can be recommended, even if based on healthy volunteer studies under accelerated approval, an adequately controlled trial in the target population is necessary to fully characterize the safety and efficacy of the product. To date, FDA has not reached agreement with the applicant on an adequately designed confirmatory study. Portola agreed to conduct a Usual Care Cohort prospective study that would serve as a historical control for the ongoing confirmatory study; however, a final protocol has not been approved. Furthermore, revisions to the confirmatory study are required to ensure more interpretable data (see sections 6.3.3 and 6.3.11).

Benefit-Risk

Serious or life-threatening bleeding is a labeled adverse reaction of FXa inhibitors. The applicant estimates that >100,000 patients treated with FXa inhibitors will have a serious or life-threatening bleed annually in the US. Currently there are no approved therapies for the reversal of the anticoagulant effect of direct FXa inhibitors. In patients experiencing a major bleeding event, current consensus-based guidelines recommend withdrawing the anticoagulant and providing "routine usual supportive care including fluid resuscitation, red blood cell transfusions, maintenance of renal function, identification of bleeding source, and surgical intervention as needed. Consideration of the use of PCC, activated PCC or rFVIIa is also recommended; however, there is limited available data supporting the efficacy of these non-specific drugs for this indication. The availability of a reversal agent would increase treatment options by providing a more targeted therapy.

Risks

The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of FX inhibitors and antibodies against CHO (b) (4) . The ability to clearly define these risks in the target population and for this product is limited by the size of the safety database. Furthermore, the applicant did not investigate for antibodies against CHO (b) (4) . However, of the 57 subjects treated in the ongoing confirmatory study (14-505), no subjects were positive for FX antibodies. Most infusion-related reactions were mild and resolved without incident. Of the 16 reported thrombotic events in 9 subjects, 2 were considered related to the product by this reviewer. Of the 37 SAEs that were reported in 18 subjects, one (ischemic stroke) was considered related. The potential for these risks should be discussed in a boxed warning and the Warnings and Precautions sections of the Package Insert if the product is eventually approved.

Benefits

The benefit of this product derives from its ability to reverse anticoagulation. The efficacy of Andexxa for a limited indication of reversal of direct FXa inhibitors apixaban and rivaroxaban in life-threatening or uncontrolled bleeding has been demonstrated by data from healthy volunteer studies demonstrating that Andexxa can effectively reverse anticoagulation for the duration of the infusion as evidenced by reduction in anti-FXa

activity. These conclusions were supported in part by preliminary data from the confirmatory study, which demonstrated that for bleeds with anticoagulant levels in the therapeutic range, Andexxa can effectively reverse anticoagulation.

For apixaban, efficacy was demonstrated in 122 subjects enrolled in clinical trials of Andexxa, including 46 (38%) that were studied with the proposed licensed dose. At all doses studied (90 to 900 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. In general, anti-FXa activity returned to placebo levels within 2 hours after completion of administration and for subjects dosed within the therapeutic range in the phase 3 study, Andexxa resulted in >90% reduction in anti-FXa activity.

For rivaroxaban, efficacy was demonstrated in 95 subjects enrolled in in clinical trials of Andexxa, including 44 that were studied with the proposed licensed dose. At all doses studied (210 to 1760 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. In general, anti-FXa activity returned to placebo levels within 2 hours after completion of administration and for subjects dosed within the therapeutic range in the phase 3 study, Andexxa resulted in >90% reduction in anti-FXa activity. However, as noted above, 20% of subjects dosed within the therapeutic range had less-than-expected reduction in anti-FXa activity levels which was not seen with Apixaban and suggests that the higher dose may be more effective as a reversal agent.

Results from preliminary data from the ongoing confirmatory study in patients being treated with FXa inhibitors and experiencing life-threatening bleeding may be consistent with clinical benefit in that 24/31 (77%) received excellent or good efficacy ratings. However, in the absence of control data the clinical significance of these findings is questionable.

In summary, the benefits of this product are due to its efficacy in reversing anticoagulation as evidenced by reduction in anti-FXa activity, the preliminary hemostatic efficacy results in the target population and consideration of the unmet medical need. The thrombotic risks from reversal of anticoagulation can be significant and clinicians will have to weigh these risks against the potential benefits before prescribing this drug.

This product is Orphan designated 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) "; therefore pediatric studies were not required. The safety and efficacy of Andexxa in the pediatric population has not been studied.

If approved under Acelerated Approval, the ongoing study in bleeding patients (protocol 14-505) will be considered a confirmatory postmarketing requirement study under accelerated approval regulations in accordance with 21 CFR 601.41, Subpart E: "Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is

uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway." At this time, a Risk Evaluation and Mitigation Strategy is not required.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Table 1: Demographic Information of Patients Enrolled in Efficacy Studies

	Study 14-503		Study 14-504		Study 12-502			Study 14-506*		Study 14-505 (n=32)
	Part 1 (n=33)	Part 2 (n=32)	Part 1 (n=41)	Part 2 (n=39)	Mod 1 (n=54)	Mod 2 (n=48)	Mod 3 (n=27)	Younger (n=10)	Older (n=10)	
Age, years										
Mean	60.4	59.4	55.2	57.3	33.2	35.8	33.7	33.1	67.4	76.8
Median (range)	59 (50-73)	56.5 (50-73)	55 (50-65)	57 (50-68)	33 (19-44)	37.5 (19-45)	34 (21-45)	32.5 (26-42)	67.5 (65- 69)	79 (55- 95)
Gender, %										
male	57.6	68.8	63.4	56.4	85	81	63	50	50	53
female	42.4	31.2	36.6	43.6	15		37	50	50	47
Race, %										
White	100%	90.6	78.0	71.8	96	90	93	40	50	84
Black/AA	-	6.3	14.6	25.6	4	6	7	30	20	16
Asian	-	-	2.4	2.6		-	-	30	30	-
AI/Alaska Native	-	-	-	-		4	-	-	-	-
Other			4.9			-	-	-	-	-
Ethnicity, %										
Hispanic/Latino	42.4	40.6	31.7	35.9	80	79	85	10	10	6
Non-Hispanic/Latino	57.6	59.4	68.3	64.1	20	21	15	90	90	94

AA = African American AI=American Indian
*younger=18-45 years; older ≥65 years
Adapted from 125586/0, *Summary of Clinical Efficacy*, page 101/150

Reviewer Comment: Subjects enrolled in the phase 3 healthy volunteer clinical trials (14-503 and 14-504) of Andexxa were older (50-73 years old), but were notably younger than the study population of bleeding patients that is currently enrolled in the confirmatory study (14-505). Because advanced age is known to impact bleeding outcomes, the healthy volunteer data alone may not be sufficient to characterize the safety and efficacy of the product in the target population; data in the bleeding patients are needed. The enrolled population of the confirmatory study may be an adequate representation of the broader population targeted by the proposed indication; however, the sample size is too small to state this with certainty. The numbers of patients and racial breakdown are too small to make any meaningful conclusions as to the role of age or race in the treatment of Andexxa. There is no racial or ethnic predilection reported with bleeding outcomes; therefore there is no expectation of different efficacy based on gender or ethnicity.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

In the United States, direct FXa inhibitors such as rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) are approved for the prevention and treatment of thrombosis. These drugs are small molecules that bind directly to activated factor X (Xa) and neutralize their activity. They have many of the same indications as the vitamin K

antagonists, like wafarin. These drugs have a number of advantages over warfarin, including a predictable response, no need for monitoring or dose changes and fewer drug and food interactions.

Rivaroxaban was initially approved for marketing in November 2011 and is currently indicated[1]:

- To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).
- For the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), and for the reduction in the risk of recurrence of DVT and of PE
- For the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

Apixaban was initially approved for marketing in December 2012 and is currently indicated[2]:

- To reduce the risk of stroke and systemic embolism in patients with NVAF.
- For the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery.
- For the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy.

Edoxaban was initially approved for marketing in January 2015 and is currently indicated to reduce the risk of stroke and systemic embolism in patients with NVAF[3].

Serious or life-threatening bleeding is a labeled adverse reaction of these FXa inhibitors. Serious and fatal bleeding was reported in the phase 3 trials conducted to support licensure at an annualized rate of 2.1 to 3.5%, as well as in MedWatch and as anecdotal cases in literature reports[4,5,6]. The applicant states that "based on the published incidence of major bleeding in multiple Phase 3 studies with FXa inhibitors and their projected uptake, it is estimated that greater than 100,000 patients treated with these agents will suffer a serious life-threatening bleed annually in the US."

A meta-analysis of phase 3 clinical trials evaluating the safety and efficacy of novel oral anticoagulants compared to warfarin for thromboprophylaxis in atrial fibrillation reported that the use of novel oral anticoagulants was associated with a lower risk of major bleeding (relative risk [RR] = 0.79; 95 % confidence interval [CI] 0.67–0.93) and

1 XARELTO, [package insert]. Titusville, New Jersey: Janssen Pharmaceuticals, Inc., 2014.
2 ELIQUIS, [package insert]. Princeton, New Jersey: Bristol-Myers Squibb Company, 2014.
3 SAVAYSA, [package insert]. Parsippany, NJ: Daiichi Sankyo, Inc. 2015.
4 Chaudhry, M. Drowning in blood: A rare but fatal complication of rivaroxaban. *Critical Care Medicine*, 2012. 40(12 Suppl 1): p. 316.
5 Kiraly, A., *et al.* Management of hemorrhage complicated by novel oral anticoagulants in the emergency department: Case report from the northwestern emergency medicine residency. *Am J Therap*, 2013. 20(3): p. 300-306.
6 Malhotra, A, *et al.* Fatal bleeding associated with Rivaroxaban in patient with gastric lymphoma. *J Case Reports Pract*, 2013.

intracranial hemorrhage (ICH) (RR = 0.49, 95 % CI 0.37–0.63)[7]. A separate meta-analysis reported reduced risk of major bleeding with rivaroxaban (RR = 0.55, 95 % CI 0.35–0.89) and apixaban (RR = 0.31, 95 % CI 0.15–0.62) compared to warfarin for treatment of acute venous thromboembolism (VTE)[8]. However, unlike warfarin and other vitamin K antagonists, there are no specific antidotes available to reverse the anticoagulant effect of direct FXa inhibitors. Additionally, routine coagulation tests (e.g., (b) (4)) cannot be used to determine the degree of anticoagulation, making it more difficult to determine when the anticoagulant effect has worn off. Because of their pharmacokinetics, especially their wide therapeutic window, predictability and short half-life, there is debate as to how important is a reversal agent.[9] However, with increased use of these drugs, and resultant increased reports of life threatening bleeding, there remains an unmet medical need in patients using these oral anticoagulants who need immediate reversal of the anticoagulant effect.

Furthermore, although the risk of intracranial bleeding has been shown to be reduced with some novel oral anticoagulants, morbidity and mortality remain high. The characteristics and natural history of direct FXa-associated ICH are largely unknown. Traditionally, predictors of outcome in ICH have been hematoma volume, glascow coma scale, intraventricular extension, age, location, increased cerebral edema (evidenced by midline shit, herniation) and hematoma expansion.[10,11] Three large randomized clinical trials of apixaban, rivaroxaban and the direct thrombin inhibitor dabigatran reported an ICH mortality between 43% and 67%; most survivors had permanent disability[12,13,14]. Results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial showed that major bleeding in patients with atrial fibrillation is associated with substantially increased risk of death, ischemic stroke, or MI; these risks are higher following ICH. In that study, major bleeding occurred in 848 individuals (4.7%); of the 176 with ICH, 76 (43.2%) died within 30 days of the bleeding, which was considerably higher than the 9.2% of the 695 patients with major non-ICH bleeding who died. Overall, the risk of death, ischemic stroke, or MI was increased

7 Providencia R, *et al*. A meta-analysis of phase III randomized controlled trials with novel oral anticoagulants in atrial fibrillation: comparisons between direct thrombin inhibitors vs. factor Xa inhibitors and different dosing regimens. *Thromb Res*. 134(6):1253–1264.
8 Castellucci LA, *et al.* Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA* 312(11):1122–1135.
9 Eerenberg ES, *et al*. Contra: antidotes for novel anticoagulants—do we really need them. *Thromb Haemost*. 108:623–624.
10 Manno EM, *et al*. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. *Mayo Clin Proc*. 2005 Mar;80(3):420-33.
11 Garibi J, *et al*. Prognostic factors in a series of 185 consecutive spontaneous supratentorial intracerebral haematomas. Br J Neurosurg. 2002 Aug;16(4):355-61.
12 Held, C, *et al*. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. *Eur Heart J*. 2015; 36(20): p. 1264-72.
13 Hankey GJ, *et al.* ROCKET AF Steering Committee and Investigators. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation. *Stroke*. 2014;45(5):1304-1312.
14 Hart RG, *et al*. Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke*. 2012;43(6):1511-1517.

roughly 12-fold after a major non-ICH bleeding event within 30 days; however, the risk of death following an ICH was significantly increased, with HR 121.5 (95% CI 91.3–161.8) as was stroke or MI with HR 21.95 (95% CI 9.88–48.81), respectively. The study did not observe significant differences between apixaban and warfarin with respect to death or thrombotic events after a bleed.

In a small multicenter, prospective study, researchers compared 52 patients with ICH while taking warfarin with 11 patients with ICH while taking direct oral anticoagulants (6 on rivaroxaban, 3 on dabigatran, and 2 on apixaban) and found that median ICH volume was significantly larger with warfarin than with the oral anticoagulants (8.9 vs. 2.4 mL). In analyses adjusted for potentially confounding variables, at hospital discharge warfarin patients had significantly worse functional outcomes than did patients treated with direct oral anticoagulants[15].

In a prospective multicenter observational study of 61 patients on novel oral anticoagulants with ICH and sequential imaging for the hematoma expansion analysis, 45 subjects were evaluable for hematoma expansion.[16] Substantial hematoma expansion occurred in 38% (17 of 45). New or increased intraventricular hemorrhage was observed in 18% (8 of 45). Overall mortality was 28% (17 of 60 [follow-up data were missing in 1 patient]) at 3 months, and 65% (28 of 43) of survivors had an unfavorable outcome (modified Rankin Scale score, 3-6). Overall, 57% (35 of 61) of the patients received prothrombin complex concentrate, with no statistically significant effect on the frequency of substantial hematoma expansion (43% [12 of 28] for prothrombin complex concentrate vs 29% [5 of 17] for no prothrombin complex concentrate, $p = 0.53$), or on the occurrence of an unfavorable outcome (modified Rankin Scale score, 3-6) (odds ratio, 1.20; 95% CI, 0.37-3.87; $p = 0.76$).

The lack of effective treatment strategies to reverse the effect of anticoagulation and improve the overall outcome in ICH (reduce hematoma expansion, related mass effect and midline shift) is a significant public health concern.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Currently there are no approved therapies for the reversal of the anticoagulant effect of direct FXa inhibitors. In patients experiencing a major bleeding event, current consensus-based guidelines recommend withdrawing the anticoagulant and providing "routine usual supportive care including fluid resuscitation, red blood cell transfusions, maintenance of renal function, identification of bleeding source, and surgical intervention as needed."[17,18]

15 Wilson D, *et al*. Volume and functional outcome of intracerebral hemorrhage according to oral anticoagulant type. Neurology 2016 Jan 26; 86:360.
16 Purrucker J, *et al*. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. *JAMA Neurol.* 2016;73(2):169-177.
17 Siegal DM. Managing target-specific oral anticoagulant associated bleeding including an update on pharmacological reversal agents. *J Thromb Thrombolysis.* 2015 Apr;39(3):395-402.
18 Kaatz S, *et al*. Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors. *Am J Hematol* 2012; 87 Suppl 1:S141.

Consideration of the use of prothrombin complex concentrate (PCC), activated PCC or recombinant factor VIIa (rFVIIa) is also recommended; however, there is limited available data supporting the efficacy of these non-specific drugs for this indication (see Table 2 below). Also, these agents are associated with an increased risk of thrombosis so their use is limited in this patient population that has an increased risk for thrombosis at baseline.

Table 2: Published studies of non-specific agents for reversal of oral factor Xa inhibitor anticoagulant effect in animals and humans.

Reversal strategy	Animal studies (factor Xa inhibitor-treated animals)	Ex vivo studies (factor Xa inhibitor-treated volunteer or patient plasma)	Human studies (factor Xa-inhibitor-treated volunteers)
PCC	*Rivaroxaban*	*Rivaroxaban*	*Rivaroxaban*
	Corrected aPTT [48]	Corrected PT [13]	Corrected PT [9]
	Variably corrected PT [48, 49]	Variably corrected TG indices [13, 25]	Corrected PT (4-PCC > 3-PCC) [10]
	No reduction of blood loss in rabbits [48]	No correction of anti-Xa activity [13]	Corrected some TG indices (3-PCC > 4-PCC) [10]
			No effect on aPTT, anti-Xa activity [10]
	Reduced bleeding time in rats, but not primates [49]		*Edoxaban*
	Apixaban		Reversal of prolonged bleeding duration and bleeding volume after punch biopsy (50 IU/kg) dose [11]
	No correction PT [50]		
	No reduction hepatosplenic blood loss in rabbits [50]		
aPCC	*Rivaroxaban*	*Rivaroxaban*	
	Corrected aPTT [48]	Corrected PT [13]	
	Variably corrected PT [48, 49]	Corrected TG indices [13, 25]	
	No reduction of blood loss in rabbits [48]	No correction of anti-Xa activity [13]	
	Reduced bleeding time in rats and primates [49]		
	Edoxaban		
	Reduced bleeding time in rats [12]		
rVIIa	*Rivaroxaban*	*Rivaroxaban*	
	Corrected PT [49]	Corrected PT [13]	
	Reduced bleeding time in rats, but not primates [49]	Variably corrected TG indices [25]	
		No correction anti-Xa activity [13]	
	Apixaban		
	Corrected PT [50]		
	No reduction hepatosplenic blood loss in rabbits [50]		
	Edoxaban		
	Reduced bleeding time in rats [12]		

Adapted from [47]. *aPTT* activated partial thromboplastin time, *aPCC* activated prothrombin complex concentrate, *ETP* endogenous thrombin potential, *INR* international normalized ratio, *LT* lag time, *PCC* prothrombin complex concentrate, *PT* prothrombin time, *rVIIa* recombinant activated factor VII, *TEM* thromboelastometry, *TG* thrombin generation, *TP* thrombin potential, *TTP* time to peak

Source: Siegal (*J Thromb Thrombolysis* 2015; Table 3)

2.3 Safety and Efficacy of Pharmacologically Related Products

There are no licensed recombinant FX products. The only licensed FX product is COAGADEX, which is a plasma-derived FX concentrate purified from Source Plasma of US origin. It is indicated for the treatment of hereditary FX deficiency, but not for reversal of anticoagulation.

Andexxa is expressed in a Chinese Hamster Ovary (CHO) cell line, which is well characterized. Each reconstituted vial contains 100 mg of Andexxa, and the inactive

ingredients tromethamine (Tris), L-arginine hydrochloride, sucrose, mannitol, and polysorbate 80. Per the applicant, the current reconstituted lyophilized formulation contains 2% sucrose and 5% mannitol as excipients. The total amount of sucrose and mannitol are provided in Table 3 below.

Table 3: Total Amount of Mannitol and Sucrose in Andexxa

Andexxa Dose Bolus/infusion rate	Mannitol Administered (g)	Sucrose Administered (g)
400 mg /4 mg/min for 120 min	4.5	1.8
800 mg /8 mg/min for 120 min	9.0	3.6

The development of activity-neutralizing antibodies (inhibitors), binding antibodies to (b) (4), allergic reactions and pathogen transmission are the main safety concerns of treatment. The risk of viral transmission has been mitigated by viral inactivation procedures.

Reviewer Comment: Sucrose has been associated with acute kidney injury in intravenous (IV) immune globulin products, necessitating a boxed warning. The levels of sucrose in the highest single dose of Andexxa administered in the Phase 3 and ANNEXA 4 studies are within FDA's accepted range for product specifications; however, repeat dosing and longer infusions may result in sucrose levels that are similar to those associated with acute kidney injury. Portola plans to study longer fusions (up to 4 hours) as part of a (b) (4) study. FDA advised Portola to introduce specifications for sucrose and mannitol by August 1, 2016, rather than monitor the concentrations of excipients with in-process control and surrogate assays. Portola responded, in part, that "In the Phase 1-3 studies in healthy volunteers and in the > 100 bleeding patients treated in ANNEXA-4, there have been no sensitivity issues that have been specifically linked to the tolerability of sucrose or mannitol" which is misleading because based on the data and current study protocol submitted, serum chemistries in the confirmatory study (ANNEXA-4) are only done at baseline, which is inadequate to assess sucrose-related renal toxicity.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

There is no previous human experience with Andexxa.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Summary of Pre-submission Regulatory Activity

Note: This list highlights key regulatory activity, and is not an exhaustive list of interactions with Portola

May 15, 2009:	Portola submitted an initial Pre-IND Meeting Briefing Document to the Division of Blood Applications on, which stated that the product was designed as a potential reversal agent to the small molecule FXa inhibitors, specifically rivaroxaban. In its June 12, 2009 reply to the submission, FDA stated that discussion of product development, including the unmet medical need for such an agent, was premature since rivaroxaban was under review in the Center for Drug Evaluation and Review (CDER) and not yet approved.
March 6, 2012:	Portola originally submitted an IND on but subsequently withdrew the submission on April 5, 2012 based on FDA feedback.
April 23, 2012:	Portola re-filed Investigational New Drug (IND) 15089 on and received notification on April 27, 2012 of the biologic product name and IND number.
July 10, 2012:	Portola was advised that the phase 1 study could be initiated and that the use of pharmacodynamic (PD) measures as the primary efficacy endpoint for a phase 3 study to support licensure was under internal discussion.
October 18, 2012:	End of phase 1 meeting. FDA stated that: 1) the mechanism of TFPI inhibition was not adequately taken into consideration and advised to include a plan to monitor thrombotic events; 2) agreement to the continued dosing should not be interpreted to mean that the proposed design of the Phase 3 study in healthy volunteers is endorsed by the FDA. The utility of the design of the phase 3 study will be determined after review of the data from Proof of Concept study; 3) a randomized controlled trial (RCT) may take several years to complete, however safety concerns related to thrombosis need further evaluation; 4) the submitted development plan did not include a clinical trial design which would provide substantial evidence of efficacy and confirm the use of any surrogate endpoint which might be used to support an accelerated approval. FDA reminded Portola that a definitive study to confirm efficacy is required to be initiated pre-licensure for products licensed based on the accelerated approval process. Portola stated that: 1) the planned dose of FXa inhibitors apixaban and rivaroxaban will not result in over anticoagulation in normal volunteers; 2) pharmacokinetic (PK) studies would measure anticoagulant and antidote, free and bound anticoagulant measured to aid in the determination of the appropriate dose
July 19, 2013:	In a Written Response, FDA advised that 1) the proposed manufacturing changes are considered major, 2) additional clinical and/or animal studies for product characterization may be necessary, and 3) the plan to submit the proposed CMC data at the time of BLA submission would not be acceptable.
August 14, 2013:	End of phase 2 meeting. FDA stated that: 1) there was no clinical evidence of prothrombotic effect in normal volunteers; however

	elevations of prothrombin fragment 1+2 , thrombin-antithrombin (TAT), D-dimers and TFPI changes suggest potential for thrombotic process; 2) use of surrogate markers, such as reversal of anti-FXa activity and a decrease in plasma concentration of unbound FXa inhibitor, may be suitable efficacy endpoints for the phase 3 studies, if an accelerated approval pathway is sought and asked Portola to submit evidence to show that these endpoints are reasonably likely to predict clinical outcomes in the target population; 3) the proposed clinical program may not be sufficient to support licensure as clinical trials in healthy volunteers will not evaluate whether clinical outcomes are improved for bleeding patients as a result of treatment with this product, and advised Portola to revise their clinical development plan to include clinical trials for evaluation of safety and efficacy in the target population if they are unable to provide evidence to support the use of the surrogate; 4) preliminary data in bleeding patients would be required before approval; 5) breakthrough therapy designation may expedite the development and review of the drug, but would not automatically lead to standard approval. Portola stated that a standard approval regulatory pathway based on clinical outcomes was not feasible.
November 22, 2013:	Breakthrough Therapy Designation request was acknowledged on November 4, 2013 and granted on November 22, 2013 for reversal of anticoagulant effect of direct and indirect FXa inhibitors.
December 16, 2013:	During the Type C meeting to discuss potential clinical trial designs for the confirmatory study, FDA acknowledged the unmet medical need and stated that: 1) data from one fourth to one half of patients from the Phase 4 study should be submitted in the BLA to assess the efficacy and safety of the product, and clarified that the amount of data required is dependent on the final design of the clinical trial. Portola stated that this requirement would delay their BLA submission by 2 years. An agreement on the final design of the phase 4 study was not reached.
November 7, 2014:	FDA agreed to the overall phase 3b/4 confirmatory study (protocol 14-505) design plan, but advised that failing to demonstrate a reasonable correlation between the clinical endpoint and the biomarker may impact the regulatory pathway, and if approved, the product labeling.
November 24, 2014:	Portola was advised that FDA did not agree with plans for initial commercialization with (b) (4) made by (b) (4) , the proposed strategy for process validation of the (b) (4) manufacturing process and proposed timing of the submission of the validation data for the (b) (4) process and release tests for the (b) (4) product to be used as the commercial drug product (DP), DP testing and release, DP validation and timing of submission of

	validation data, stability testing of DP, expiry dating and submission timing of data.
March 18, 2015:	FDA provided additional comments regarding the confirmatory study provided, including requests to modify the case report form (CRF) to include relevant clinical information like renal function and the efficacy endpoint of nonvisible bleeding assessment.
June 16, 2015:	Portola provided updates on the status of clinical trials (3 subjects enrolled in the phase 3b/4 confirmatory study to date) and clarifications regarding the overall clinical development program, stating that the (b) (4) study is not intended to support an efficacy supplement, but is intended as a supportive study to the confirmatory study and for a broad indication where reversal of anti-Xa effect is anticipated.
August 3, 2015	In an Advice Letter, FDA informed Portola that several major deficiencies related to a number of clinical trial design elements, including eligibility criteria, efficacy analysis, and safety were identified in the ongoing confirmatory protocol. Portola was advised that these deficiencies could adversely impact its acceptability as a confirmatory study that is required per the accelerated approval program.
September 4, 2015:	Type A meeting to confirm the study design and number of subjects required at the time of the BLA submission. Portola agrees to submit an amendment to the IND requesting the feasibility of using data collected from 10-20 subjects in their phase 3b/4 study and all data to support the use of anti-FXa as a surrogate reasonably likely to predict clinical benefit.
September 30, 2015:	Type A meeting to reach agreement on the use of anti-FXa as a surrogate to support an accelerated approval pathway. An agreement regarding an appropriate choice of control for the confirmatory study was not reached; FDA stated that Portola's plan to use control data from the Kcentra study is not an acceptable historical control.
October 6&8, 2015:	Pre-BLA meetings for CMC (10/6/2015) and clinical/non-clinical (10/8/2015).
November 13, 2015:	Type A meeting to discuss PD surrogacy for rivaroxaban, apixaban, edoxaban and enoxaparin. FDA agreed to accept a BLA for consideration for filing for edoxaban, apixaban and rivaroxaban as a "class-effect" (i.e. direct FXa inhibition), but advised that: 1) determination of safety and efficacy for approval would not be based on a "class-effect" and 2) the "rebound" in anti-FXa activity following completion of the Andexxa infusion is of concern; an appropriate target anti-FXa activity level should be identified, rather than use percent reduction as an efficacy endpoint. Portola agreed to consider evaluating additional dosing regimens, including adding an additional treatment arm (bolus plus longer than two hour infusion) to the study. No agreement was reached on

the appropriate control population for the confirmatory study. Prior to this decision on November 13, 2015, the Division at the direction of CBER management discussed on November 10, 2015, with the Division of Hematology Products (DHP) and Division of Cardiovascular and Renal Products (DCRP) at CDER, the regulatory requirements for accelerated approval. The discussion included the extent of data required to demonstrate that the surrogate endpoint was likely to predict for clinical benefit given the information[19] provided in the guidance, noting that such information was not available for Andexxa in that the determination of 'reasonably likely' was based largely on biologic plausibility without clinical data to demonstrate correlation of the PD parameters to clinical benefit. The discussion also included issues with duration and depth of reversal of anti-FXa activity following andexxa infusion as provided in the top-line results in the pre-meeting package. A decision was reached, that filing and review for regulatory decision making could be permitted based solely on the correlation between the surrogate endpoint and pharmacyodynamic parametes and that preliminary evidence of correlation between the clinical benefit endpoint and surrogate endpoint was not necessary. The discussion included citings of regulatory precedence for such an approach.

Summary of Post-submission Regulatory Activity

February 24, 2016: Type A meeting to discuss an appropriate control cohort for the confirmatory study. Portola agreed to submit a study protocol and statistical analysis plan (SAP) for a prospective cohort "usual care" study, a revised SAP for the confirmatory study and a protocol and SAP for (b) (4). To support the development of the new prospective "usual care" cohort study and a (b) (4) -study (or separate (b) (4) study protocol), FDA agreed to informal monthly teleconferences with Portola.

April 20, 2016: Type A Escalation meeting with CBER Cener Director, Dr. Peter Marks, to discuss ongoing disputes between Portola and CBER concerning scientific issues that remain unresolved, specifically use of anti-FXa activity as a surrogate, dose and dosing regimen for the ongoing confirmatory study; design of the Usual Care

19 FDA guidance *Expedited Programs for Serious Conditions – Drugs and Biologics* states "determining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease the endpoint, and the desired effect and the empirical evidence to support that relationship. The empirical evidence may include ". . . epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools. Evidence of pharmacologic activity alone is not sufficient, however. Clinical data should be provided to support a conclusion that a relationship of an effect on the surrogate endpoint or intermediate clinical endpoint to an effect on the clinical outcome is reasonably likely."

Cohort Study, lack of continuity of the review team and the review Division's decision to present Portola's application to the Blood Products Advisory Committee (BPAC) Meeting on June 20 and 21, 2016. FDA held a follow-up teleconference with Portola on April 28, 2016

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

This submission consisted of the five modules in the Common Technical Document structure. The application was sufficiently organized and integrated to allow for a complete clinical review. However, initial patient profile summaries and patient narratives from subjects enrolled in the ongoing confirmatory study (14-505) were inadequate to allow for a complete review. In response to an information request, the applicant provided updated profiles for each subject.

3.2 Compliance With Good Clinical Practices And Submission Integrity

In order to assess compliance with good clinical practices and to verify the key submitted safety and efficacy data against source documents, CBER Bioresearch Monitoring (BIMO) issued high-priority inspection assignments for two domestic sites. The two sites selected represent the clinical study sites that enrolled subjects from the two phase 3 healthy volunteer studies to support licensure (14-503 and 14-504). No BIMO inspections of study sites participating in the confirmatory study were conducted because the study is still ongoing.

The BIMO inspections of the two clinical investigators did not reveal substantive problems that impact the data submitted in the application. During the inspection it was noted that the ECG data were not stored electronically as per the study protocol, and multiple unscheduled ECG readings were collected from a number of study subjects at both clinical sites. The analyses for each of these unscheduled ECG recordings were not well documented.

Table 4: Inspection Results

PROTOCOL	SITE NUMBER	SITE LOCATION	FORM FDA 483	FINAL CLASSIFICATION
14-503	001	Celerion Tempe, Az	Not Issued	No Action Indicated
14-504	001	West Coast Clinical Trials, Inc. Cypress, CA	Not Issued	No Action Indicated

3.3 Financial Disclosures

Covered clinical study (name and/or number): 14-505, 14-504, 14-503, and 12-502		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 34 Prinicipal Investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Financial certification and disclosure information (Form 3454) have been submitted, and the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. No questions about the integrity of the data were raised.

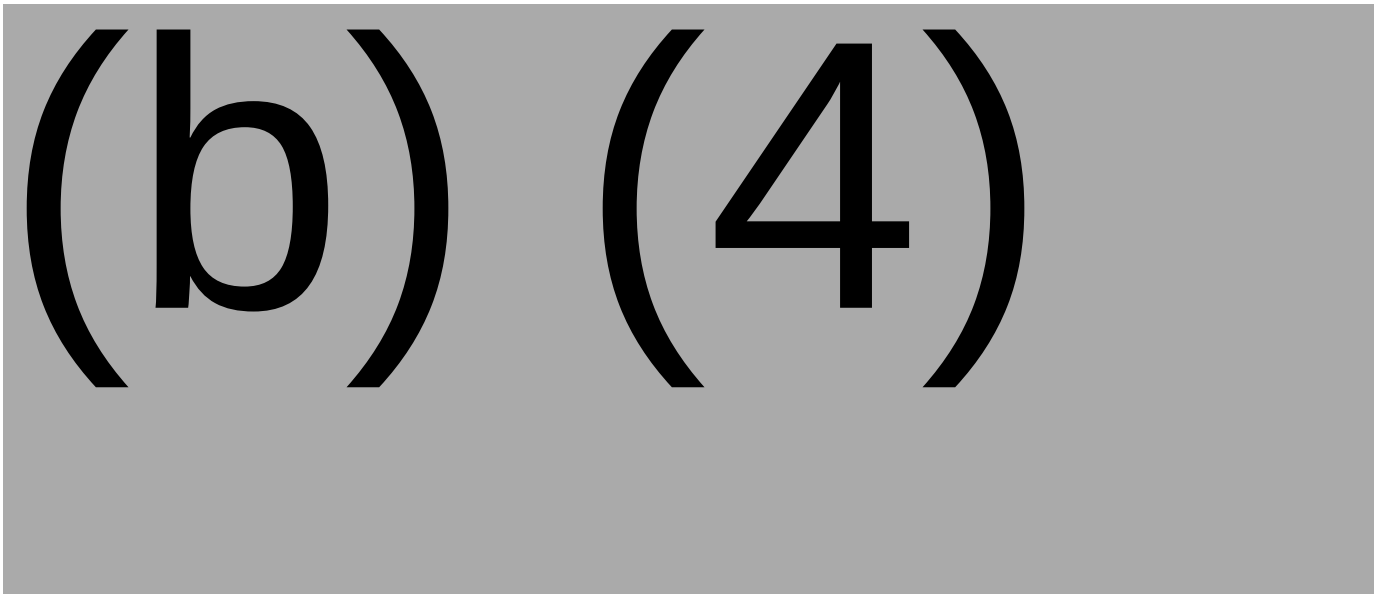
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Andexxa is a modified recombinant FXa protein composed of (b) (4) amino acids and an approximate molecular weight of 41 kDa. It is purified by traditional protein purification methods ((b) (4) step to inactivate viruses, and a (b) (4)). It is expressed in CHO cells as a processed molecule (not as a zymogen) and therefore does not require either *in vitro* or *in vivo* activation necessary for converting native FX to its activated form FXa. The molecule is (b) (4) and inactivated to lack physiologic blood

coagulation factor activity but remains capable of binding FXa inhibitors with affinity similar to that of native FXa:

- It is devoid of the γ-carboxyglutamic acid (Gla)-containing domain, which eliminates membrane binding necessary for incorporation into the prothrombinase complex.
- It lacks proteolytic activity due to a change of the active site serine residue to alanine, but still retains the ability to bind to both direct and indirect FXa inhibitors with high affinity.
- It is directly expressed as an activated FXa derivative rather than a FX precursor which eliminates the need for FVIIa or FXa activation in the circulation.
- Andexxa also binds to and inactivates TFPI, an endogenous inhibitor of blood coagulation, which leads to a faster rate of FXa generation and an elevated rate of thrombin generation and therefore may contribute to its procoagulant activity *in vivo*.



4.2 Assay Validation

See the Chemistry, Manufacturing and Controls review.

Anti-FXa activity was measured by a (b) (4) assay and thrombin generation was measured using a tissue factor-initiated thrombin generation assay. These assays were performed at a Central Laboratory.

Per the applicant, an (b) (4) detection method ((b) (4)) was used to evaluate binding antibodies to Andexxa as well as FX and FXa. Bioassays were used to determine if detected antibodies could interfere with the activity of their respective target.

Reviewer Comment: During the review, BLA chair and CMC reviewer, Dr. Mikhail Ovanesov, advised Portola of concerns that the thrombin generation assays used in

the clinical and preclinical spiking studies may not be adequately qualified for the evaluation of Andexxa's effects. Portola used two versions of the thrombin generation assay in clinical trials without qualifying these tests. The two methods were found to be non-comparable. Furthermore, as of July 13, 2016, Portola did not report TFPI activity assay qualifications, nor did they validate this assay. Dr. Ovanesov also advised that the immunogenicity program was inadequate because Portola did not test for inhibitory antibodies against FX and FXa despite their previous claims (during the IND review) of doing so. Both issues will be further evaluated in future studies.

4.3 Nonclinical Pharmacology/Toxicology

See the full Nonclinical Pharmacology/Toxicology review.

The submitted nonclinical studies and resulting data were adequate to establish the desired pharmacologic activity of Andexxa. Andexxa was tested in single and repeat dose toxicity studies in rats and monkeys with Andexxa administered alone as well as in combination with FXa inhibitors (apixaban, rivaroxaban, (b) (4) , and enoxaparin). Toxicity studies conducted in (b) (4) monkeys did not identify any unexpected findings or significant safety concerns. In a repeat-dose toxicity study, (b) (4) rats were injected twice daily for 14 days with ANDEXXA at doses of up to 2-fold greater than the clinical starting dose. There were five mortalities following ANDEXXA treatment at all the doses tested in the study and no mortalities were observed in the control group. No microscopic findings were reported to ascertain the cause of expiration. Per the applicant, "testing at the MFD (60 mg/kg/day) did not elucidate any serious adverse effects in the presence or absence of FXa inhibitors." Increases in markers of coagulation and thrombosis (e.g., TAT and D-dimer) were observed, but were not associated thrombotic events. In addition, *in vitro* studies demonstrated that the Andexxa has minimal effect on thrombin generation in the absence of the FXa inhibitor, but does enhance thrombin generation in the presence of the inhibitor. These spiking studies of plasma samples showed that thrombin generation was increased by <15% above the pre-treatment baseline.

CDER clinical pharmacology consult reviewers analyzed D-Dimer, total TFPI and free TFPI following Andexxa bolus in the presence of apixaban and rivaroxaban from the Phase 2 healthy volunteer dose-ranging study. A dose-dependent increase in D-dimer levels was observed during the first 24 hours. No dose dependent effects were observed with TFPI.

Reviewer Comment: The increases in TAT and D-dimer were attenuated when Andexxa was administered in the presence of FXa inhibitors (NC-11-0394-R0004), which is similar to what was observed in clinical studies. As discussed in Dr. Ovanesov's memo, the preclinical findings for thrombin generation were inconsistent with clinical trial results, where significant (30-60% above baseline values) and sustained elevations in thrombin generation was noted.

4.4 Clinical Pharmacology

See the full Clinical Pharmacology review.

4.4.1 Mechanism of Action

The mechanisms of action of Andexxa are sequestration of the FXa inhibitor and TFPI inhibition (procoagulant activity). Specifically, Andexxa acts as an FXa decoy molecule by binding to the FXa inhibitors and preventing them from interacting with the native FXa molecule.

In phase 1 studies, Andexxa completely inhibited TFPI activity at least 3 hours after bolus administration and returned to 25% of the pre-treatment level at 24 hours. TFPI (free) antigen was reduced to below the limit of assay detection for 24 hours. Bioanalytical studies suggested that the observed TFPI antigen decrease is explained by a complex formation between TFPI and Andexxa. Portola interpreted TFPI (free) antigen decrease as a measure of TFPI activity inhibition. TFPI activity and antigen remained inhibited for as long as 24 hours, which correlated with the prolonged elevation of thrombin generation measured by the tissue factor-activated thrombin generation assay. TFPI activity was not investigated in phase 2 and 3 studies in the presence of FXa inhibitors; however, TFPI antigen was reduced to a similar degree in both phase 1, 2 and 3 studies. TFPI antigen was reduced to a similar degree in both phase 1 and 3 studies.

Reviewer Comment: The mechanism of TFPI inhibition was not adequately evaluated during the clinical development of Andexxa. Portola initially reported that the contribution of TFPI inhibition was negligible and did not pose significant safety concerns. However, as noted above, elevations in thrombin generation above pre-inhibitor treatment levels during clinical trials of Andexxa, and Portola's subsequent admission that these elevations were in part mediated by inhibition of TFPI, suggests that duration of the procoagulant effect and the risk of thrombogenicity were not adequately characterized. To better understand the safety and efficacy of Andexaa, the contribution of TFPI inhibition, the generation of thrombin in reversing the anticoagulant effects of FXa inhibitors and the procoagulant activity of andexanet, Portola has committed to further investigations in future studies. Analytical validation of the TFPI activity is an initial step to these investigations.

4.4.2 Human Pharmacodynamics (PD)

The effects of Andexxa can be observed through changes in anti-FXa activity, free fraction of available FXa inhibitor and thrombin generation.

The reversal of anticoagulant effect is evidenced by an immediate decrease in unbound drug concentrations, which corresponds to a decrease in anti-FXa activity and indicates inactivation of the anticoagulant effect. This effect is sustained throughout the infusion of Andexxa; however, there is a rebound in anti-FXa activity and unbound drug

concentration to levels that are higher in magnitude than levels observed at 48-72 hours after cessation of anticoagulant treatment.

In addition, administration of Andexxa results in an immediate increase in the endogenous thrombin potential (ETP), with mean levels that are above the 95th percentile of baseline values. In fact, post-infusion ETP levels are within the 5th to 95th percentile interval of observed baseline values while unbound drug and anti-FXa activity is still measurable.

Reviewer Comment: Dr. Mahmood and CDER Clin Pharm consultants agree that the apparent rebound of anti-FXa activity may be mitigated with longer infusions of Andexxa. Based on these observations, FDA previously advised Portola to evaluate additional dosing and longer infusions in their clinical development program. As of the time of this review, additional dosing or infusions longer than 120 minutes had not been evaluated, so the safety and efficacy of such regiments remains unknown.

4.4.3 Human Pharmacokinetics (PK)

Distribution

The volume of distribution (Vd) for Andexxa is approximately equivalent to the blood volume of 5 L.

Elimination

Clearance for Andexxa ranges from 4 to 6 L/hr. The elimination half-life ranges from 5 to 7 hours.

4.5 Statistical

The statistical reviewer verified that the primary study endpoint analyses cited by the applicant were supported by the submitted data.

4.6 Pharmacovigilance

See Office of Biostatistics and Epidemiology review.

Portola has submitted a formal pharmacovigilance plan for monitoring safety in the post-licensure period, which includes a commitment to conduct a confirmatory postmarketing requirement (PMR) clinical trial under accelerated approval regulations in accordance with 21 CFR 601.41, Subpart E: "*Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway*."

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

This review focuses on data from two randomized, double-blind, placebo-controlled phase 3 studies (14-503 and 14-504) conducted in older healthy volunteers. In addition, supportive efficacy and safety data from an ongoing phase 3b/4 confirmatory study (14-505) in bleeding patients was reviewed. Each individual clinical study is discussed separately in section 6. Limited integrated efficacy and safety analyses are presented in sections 7 and 8, respectively.

Table 5: Review Responsibilities

Discipline Review	
Chemistry, Manufacturing and Controls Review; BLA Chairperson	Mikhail Ovanesov
Clinical Review	Lisa Faulcon
Clinical Pharmacology Review	Iftekhar Mahmood
Statistical Review	Chunrong Chen
Pharmacology / Toxicology Review	Yolanda Branch
Bioresearch Monitoring Review	Haecin Chun
Pharmacovigilance Review	Faith Barash
Labeling Review	Kristin Khuc
Regulatory Project Manager	Thomas Maruna

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following materials from the submission were considered for the review:

Volume(s)	**Information**
2.7.3	Summary of Clinical Efficacy
2.7.4	Summary of Clinical Safety
5.2	Tabular Listing of all Clinical Studies
5.3.3	Reports of Human PK Studies
5.3.4	Reports of Human PD Studies
5.3.5	Clinical Study reports
5.4	Literature References

5.3 Table of Studies/Clinical Trials

Please see the applicant's list of completed and ongoing clinical studies in Table 5 below.

Table 6: 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) 20 mg orally every 24 hours for 4 days	n=26 800 mg bolus followed by a 120 min infusion at 8 mg/min	n=13
14-505 Efficacy/ Safety	Multicenter, open-label, single arm	N=57 subjects with acute major bleeding (32 evaluable for efficacy) 77 years (47–95)	Apixaban (n=27) Rivaroxaban (n=24) Enoxaparin (n=6) Edoxaban (n=0)	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 *Recommended dose is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor*	N/A
Phase 2 Studies					
12-502 Safety, PK/PD	Single center, randomized, double-blind,	Module 1: N=54 healthy subjects	Module 1: Apixaban (n=54)	n=36 90 mg (n=6) 210 mg (n=6) 420 mg (n=6) 600 mg (n=6)	n=18

	vehicle-controlled	33 years (19-44)	5 mg orally every 12 hours for 6 days	900 mg (720 mg +4mg/min for 120 min; n=6)	
		Module 2 N=48[a] healthy subjects 36 years (19-45)	Module 2: Rivaroxaban (n=48) 20 mg orally every 24 hours for 6 days	n=30 210 mg (n=6) 420 mg (n=6) 600 mg (n=6) 600 mg (420 mg +4 mg/min for 45 min; n=6) 900 mg (720 mg +4mg/min for 60 min; n=6) 1760 mg (800 mg +8 mg/min for 120 min; n=6)	n=15
		Module 3 N=27 healthy subjects 34 (21-45)	Module 3: Enoxaparin (n=27) 40 mg subcutaneously every 24 hours for 6 days	n=18 210 mg bolus (n=12) 420 mg (n=6)	n=9
		Module 4 N=28[b] healthy subjects 33 (19-45)	Edoxaban (n=28) 60 mg orally every 24 hours for 6 days	n=18 600 mg (n=6) 800 mg (n=6) 1280 mg (800 mg + 8 mg/min for 60 min (n=6)	n=8
Phase 1 Studies					
11-501	Single center, randomized, Double-Blind, Placebo-Controlled Single Ascending Dose	Cohort 1	N/A	30 mg (n=6)	n=2
		Cohort 2	N/A	90 mg (n=6)	n=2
		Cohort 3	N/A	300 mg (n=6)	n=2
		Cohort 4	N/A	600 mg (n=6)	n=2
14-506 Safety, PK/PD	Single center, open-label	N=20 healthy subjects 50 years (26-69)	Apixaban (n=20)	Group 1 (younger subjects): N=10 400 mg bolus	N/A

			2.5 mg orally every 12 hours for 3.5 days	Group 2 (older subjects): N=10 400 mg bolus	

PK=Pharmacokinetics; PD=Pharmacodynamics
a 45 subjects were enrolled and treated with rivaroxaban; however, 3 subjects were discontinued prior to receiving Andexxa/placebo due to problems with the infusion pumps.
b 2 placebo subjects were discontinued following anticoagulant treatment and prior to placebo treatment.

5.4 Consultations

Because this application was not referred to an Advisory Committee, additional expert opinion was obtained from Special Government Employee (SGEs) and consultants within FDA to comment on the adequacy of the depth and duration of reversal of Andexxa particularly as it relates to the type of bleeding (for example, intracerebral bleeding), the clinical significance of the observed rebound in anti-FXa activity to levels that are higher than placebo for subjects anticoagulated with apixaban and rivaroxaban and the observed abnormalities in PR and QT values, the generalizability of the healthy volunteer study results to the target (bleeding) population, the need for additional premarket studies to evaluate Andexxa's use in renally-impaired patients, and the adequacy of the design of the confirmatory study to evaluate the efficacy of anticoagulant reversal in the setting of ICH.

5.4.1 Advisory Committee Meeting

This clinical reviewer recommended that this application be referred to the *Blood Products Advisory Committee* prior to product approval for the following reasons:

- The product is a new molecular entity (NME) reviewed under the accelerated approval pathway.
- Review of information submitted in the BLA raised issues that this reviewer believed were appropriate topics to be discussed at an advisory committee, including the adequacy of anti-FXa activity as a surrogate, of the proposed dosing regimen for clinical situations where prolonged reversal (>2 hours is needed), and of the limited safety and efficacy database. In addition, concerns for the "rebound" in anti-FXa activity following completion of the Andexxa infusion, the inadequacy of the immunogenicity testing (neutralizing antibodies to FX and FXa were not evaluated and retained patient samples were not available for investigation) and the inadequacy of TFPI evaluation were to be discussed in a public forum.

However, after consideration of the issues presented by the review team (clinical and CMC reviewers) the decision was made by the CBER Center Director, Dr. Peter Marks, not to refer this application to the Blood Products Advisory Committee.

5.4.2 External Consults/Collaborations

A list of the FDA and SGE consults that were obtained during the review is provided in Table 6 below. Finalized consult responses are provided in Appendix I; a final document from Division of Neurology Products was not available at the time of completion of this memo.

Table 7: Consultations

CDER	
Discipline	Reviewer
Division of Cardiorenal Products	Shari Targum
Division of Hematology Products	Lori Ehrlich
Division of Neurology Products	John Marler
Division of Clinical Pharmacology I	Jeffry Florian and Rajnikanth Madabushi
Special Government Employee	
Hematology	Donna DiMichele, MD
Hematology	Thomas Ortel, MD, PhD
Neurology	James Grotta, MD

5.5 Literature Reviewed

1. Ansell JE. Universal, class-specific and drug-specific reversal agents for the new oral anticoagulants. *J Thromb Thrombolysis.* 2016 Feb;41(2):248-52.
2. Ansell JE, *et al*. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med*. 371(22):2141–2142.
3. Broderick JP, *et al*. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993 Jul;24(7):987-93.
4. Castellanos M, *et al.* Stroke Project, Cerebrovascular Diseases Group of the Spanish Neurological Society. Predictors of good outcome in medium to large spontaneous supratentorial intracerebral haemorrhages. *J Neurol Neurosurg Psychiatry*. 2005;76:691-5.
5. Dowlatshahi, D *et al*. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. *Stroke.* 43 (2012), pp. 1812–1817.
6. Glund S, Stangier J, Schmohl M et al (2014) Idarucizumab, a specific antidote for dabigatran: immediate, complete and sustained reversal of dabigatran induced anticoagulation in elderly and renally impaired subjects. *Blood*.124(21):344.
7. Kasliwal M. Outcome following intracranial hemorrhage associated with novel oral anticoagulants. J Clin Neurosci. 2015 Jan;22(1):212-5.Mayer, SA, *et al*. Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage. NEJM, 2005. 352(8):777-85.
8. Levy JH, *et al*. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC and the ISTH. *J Thromb Haemost*. 2016; 14: 623-7.
9. Pernod, G, *et al.* Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants,

thrombin or factor-Xa inhibitors: proposals of the working group on perioperative haemostasis (GIHP) - March 2013. *Arch Cardiovasc Dis*, 2013. 106: 382-93.
10. Sarich TC, *et al.* Novel oral anticoagulants and reversal agents: Considerations for clinical development. *Am Heart J*. 2015 Jun;169(6):751-7.
11. Sarode R, *et al*. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation*. 2013 Sep 10;128(11):1234-43.

6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1

Note to the reader: andexanet is the same product as Andexxa

14-503: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study In Older Subjects To Assess Safety And The Reversal Of Apixaban Anticoagulation With Intravenously Administered Andexanet

6.1.1 Objectives

Primary efficacy objective:
− To compare Andexxa and placebo with respect to reversal of apixaban anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion.
• Secondary efficacy objectives:
− To compare reversal of apixaban anticoagulation between Andexxa and placebo as measured by apixaban free-fraction, both after a bolus and after a bolus followed by a continuous infusion.
− To compare reversal of apixaban anticoagulation between Andexxa and placebo as measured by restoration of thrombin generation, both after a bolus and after a bolus followed by a continuous infusion.
• Safety objective:
− To assess the safety of Andexxa in subjects anticoagulated with apixaban (i.e., including bleeding events, thrombotic events, and immunogenicity), both after a bolus and after a bolus followed by a continuous infusion.

6.1.2 Design Overview

Andexxa is being 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."

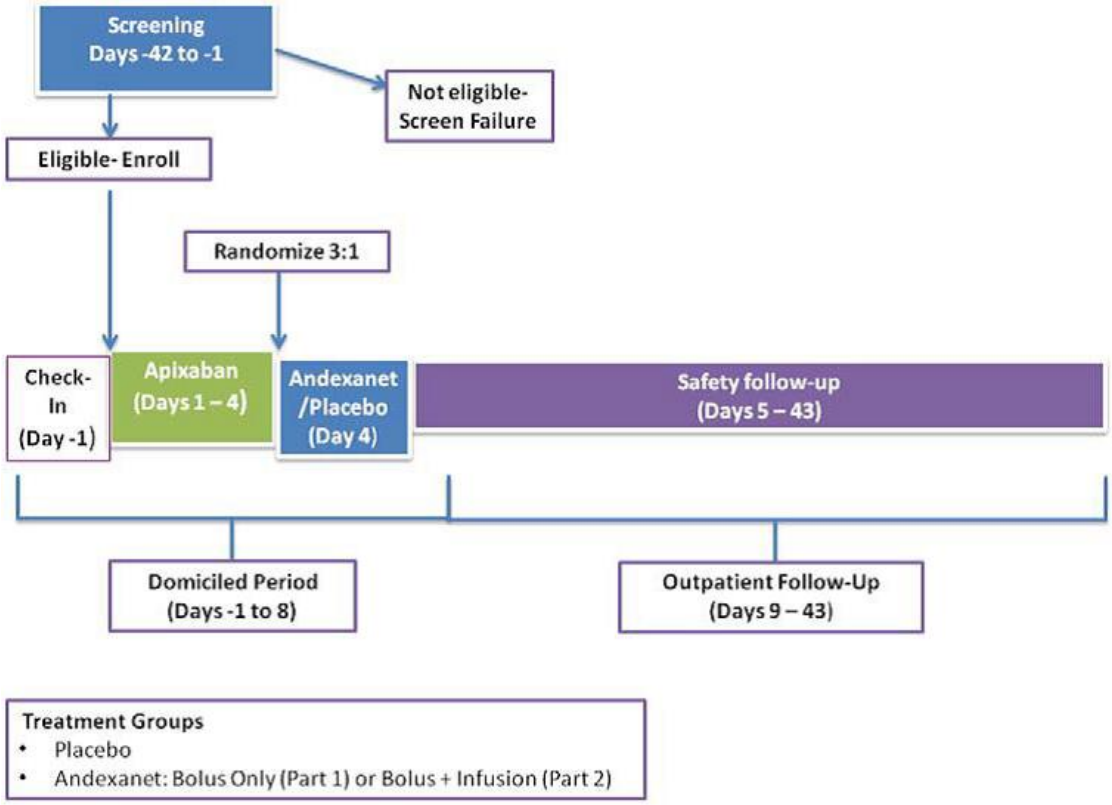
In the clinical development program for Andexxa, Trial 14-503 was one of two trials that served as the primary evidence to support safety and efficacy of Andexxa and was conducted as a randomized, double-blind, placebo-controlled study of older healthy

subjects (ages 50–75 years) who were dosed to steady-state with apixaban and then given Andexxa at the approximate steady-state maximum plasma concentration (Figure 2). Two dosing regimens of Andexxa were evaluated: bolus only (Part 1) and bolus followed by a continuous infusion (Part 2). Reversal of anticoagulation was evaluated by reduction anti-FXa activity (primary efficacy endpoint), and reduction in unbound apixaban plasma levels and thrombin generation (secondary efficacy endpoints).

Sixty-six subjects were randomized 3:1 Andexxa:placebo, domiciled at the study site for 8 days, and subsequently followed for safety through Day 43. Subjects remained on study for approximately 8 to 12 weeks, depending on the length of screening. The study periods were as follows:

- Screening: Days -42 to -1
- Anticoagulant Dosing: Days 1 to 4
- Andexxa/placebo Dosing: Day 4
- Safety Follow-Up: Days 5 to 43 (+3)

Figure 2: Trial 14-503 Design



Source: Clinical Study Report, Study 14-503, page 19 of 141.

Reviewer Comment: This study is reasonably well designed to demonstrate that Andexxa can reverse the anticoagulant effects of apixaban in normal healthy volunteers as evidenced by a decrease in anti-FXa activity. The ideal clinical trial design to evaluate the safety and efficacy of Andexxa for the proposed indication would have been a RCT in patients experiencing life-threatening bleeding and

requiring urgent/emergent reversal of anticoagulation. However, Portola claimed that such a trial design was not feasible for ethical and practical reasons: 1) it would take several years to conduct a trial using standard clinical trial approaches; 2) it would be unethical to randomize acutely bleeding acutely bleeding patients to no treatment when a potentially effective treatment is available; 3) there are a number of confounders in assessing response to therapy, therefore identifying a suitable primary clinical-outcomes-based endpoint would be challenging. This sentiment was published in a white paper from the April 22, 2014 Anticoagulant-Induced Bleeding and Reversal Agents Think Tank co-sponsored by the Cardiac Safety Research Consortium and the FDA (Sarich *et al)*.

Therefore, Portola's clinical development plan was based on achieving an accelerated approval using healthy volunteer studies. In consideration of an optimal clinical development program and pivotal clinical trial design, FDA acknowledged the challenges of designing and executing a RCT, considered the patient heterogeneity of life-threatening bleeding presentations with respect to the underlying lesions and pathology in patients on direct FXa inhibitors and the limitations of interpreting data from a single arm study, and weighed this against the ongoing unmet medical need from the absence of a reversal agent and its impact on public health. FDA determined that in addition to the PK/PD studies demonstrating reversal of anticoagulant effects, clinical data were required to support approval; these data could be obtained from healthy volunteer studies under an accelerated approval pathway, providing that some supportive data from bleeding patients was also included in the BLA submission. FDA also requested, and the applicant agreed, to conduct a usual care cohort study in bleeding patients receiving direct FXa inhibitors in which subjects could receive any commercially available product the investigators thought appropriate, to serve as a control for the ongoing phase 3b/4 single-arm trial evaluating andexanet in bleeding patients. As of the time of this review, the applicant has not submitted a version of the usual care cohort study to which FDA has agreed regarding the design.

6.1.3 Population

Important Eligibility Criteria

Inclusion Criteria

- The subject must be in reasonably good health as determined by the Investigator based on medical history, full physical examination (including blood pressure [BP] and pulse rate measurement), 12-lead electrocardiogram (ECG), and clinical laboratory tests. Subjects with well-controlled, chronic, stable conditions (e.g., controlled hypertension, non-insulin dependent diabetes, osteoarthritis, hypothyroidism) may be enrolled based on the clinical judgment of the Investigator and if approved by the Medical Monitor.
- The subject must be between the ages of 50 and 75 years, inclusive, at the time of signing of the ICF.
- The subject agrees to comply with the contraception and reproduction restrictions of the study.

- The subject must have a systolic blood pressure (SBP) <160 mmHg and diastolic blood pressure (DBP) <92 mmHg at Screening and Day -1.
- The following laboratory values must be within the normal laboratory reference range within 28 days of Day -1:
  − (b) (4)
  − Hemoglobin, hematocrit, and platelet count.
- The following laboratory values must be equal to or below 2 times the upper limit of normal (ULN) range within 28 days of Day -1:
  − Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and total bilirubin.
- The Screening serum creatinine must be below 1.5 mg/dL within 28 days of Day -1.
- The subject has a body mass index of 19 to 32 kg/m^2, inclusive, and weighs ≥60 kg.

Exclusion Criteria

- The subject has a history of abnormal bleeding, signs or symptoms of active bleeding, or risk factors for bleeding.
- The subject has a stool specimen that was positive for occult blood within 6 months of study Screening or during the Screening Period.
- The subject has past or current medical history of thrombosis, any sign or symptom that suggests an increased risk of a systemic thrombotic condition or thrombotic event, or recent events that may increase risk of thrombosis.
- The subject has an absolute or relative contraindication to anticoagulation or treatment with apixaban.
- The subject has taken (by any route) ≥1 doses of aspirin (including baby aspirin), salicylate or subsalicylate, other antiplatelet drugs (e.g., ticlopidine, clopidogrel), nonsteroidal anti-inflammatory drugs, fibrinolytic, or any anticoagulant within 7 days prior to Day -1 or is anticipated to require such drugs during the study.
- The subject has been receiving (by any route) hormonal contraception, postmenopausal hormone replacement therapy (HRT) (including over-the-counter products), or testosterone during the 4 weeks prior to Study Day -1 or is anticipated to require such drugs during the study.
- The subject has a family history of or risk factors for a hypercoagulable or thrombotic condition, including one of the following:
  − Factor V Leiden carrier or homozygote;
  − Protein C, S, or antithrombin III (ATIII) activity below the normal range.
- Use of any drugs that are strong dual inhibitors or inducers of CYP3A4 and P-gp within 7 days prior to Study Day -1 or anticipated need for such drugs during the study.
- The subject has participated in an investigational drug study within 30 days of Day -1 or Day -1 is within 5 half-lives of the investigational compound.
- The subject has a medical or surgical condition that may impair drug (anticoagulant or Andexxa) metabolism.

- The subject is allergic to any of the vehicle ingredients: tris, arginine, sucrose, hydrochloric acid, mannitol, and polysorbate 80.
- Subject is breastfeeding or has a positive pregnancy test at Screening or Day -1.

Reviewer Comment: A healthy volunteer study population was considered suitable for the demonstration of reversal of anticoagulation because it was considered feasible to achieve therapeutic anticoagulation in this population and to directly measure its reversal using assays for anti-FXa activity. Phase 3 clinical trials of direct FXa inhibitors have demonstrated that advanced age, poor renal function, and low body weight are all associated with elevated drug levels, and elevated drug levels are associated with an increased risk of bleeding. Therefore, while the inclusion of older patients is appropriate, the exclusion of patients with renal insufficiency may result in issues of generalizability to the target population since these patients may have a different bleeding/re-bleeding profile. Furthermore, patients at risk for thrombosis were excluded so the potential prothrombotic effects cannot be fully realized by this study population. The limitations of this database do not undermine the conclusions about safety and efficacy of Andexxa in that it is feasible to generalize these results to patients with normal renal function who are experiencing bleeding within the therapeutic range of anti-FXa studied; however, the limitations highlight the importance of obtaining data in the bleeding population. The most informative population to evaluate the impact of renal insufficiency and the risk of thrombosis is in the target population. The CDER DHP consultant agreed, stating that "an understanding of the pharmacokinetics in the renally impaired population would be important."

It is important to note that Andexxa is not renally cleared, thus dose adjustments to Andexaa to minimize thrombosis risks from Andexxa may not be necessary. However, because the rate of elimination of some direct FXa inhibitors is slower in renally impaired subjects, a prolonged PD effect may be required, which could likely be achieved by longer infusions; however, the safety of longer infusions has not been evaluated.Therefore studies in the renally impaired population are needed to inform about Andexxa's efficacy and safety in the setting of reduced clearance of the anticoagulant and in a patient population that is at higher risk for thrombosis due to the underlying disease status.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were administered apixaban 5 mg orally every 12 hours for 3.5 days (to steady state; Day 1 to 4) and then administered Andexxa or placebo. Andexxa was administered as a 400 mg bolus or as a 400 mg bolus followed by a 4 mg/min x 120 min infusion. Placebo was administered as an intravenous bolus over approximately 13 minutes (Part 1) or as a bolus over approximately 13 minutes followed by a continuous infusion for 120 minutes (Part 2). For both dosing regimens, the bolus was started 3 hours after the last apixaban dose (at the approximate steady-state maximum plasma concentration).

Reviewer Comment: The applicant states that "The dose for this Phase 3 study was chosen based on nonclinical animal model data and data from the Phase 2 study (12-

502). The doses in this study are equivalent to the highest doses studied in the Phase 2 study with apixaban, in which decreases in anti-FXa activity that resulted in normalization of hemostasis as measured by thrombin generation."

This clinical trial did not evaluate the efficacy and safety of the "high dose" Andexxa (800 mg bolus, 8 mg/min x 120 min), which Portola is proposing to include as a labeled dose for apixaban. Extrapolation of efficacy from the healthy volunteer study in which subjects were anticoagulated with rivaroxaban is not acceptable given the differences in PK/PD and *in-vivo*/*ex-vivo* (e.g., ED50, etc.) parameters between the two anticoagulants; because of the potential for a prothrombotic state as a result of Andexxa's dual mechanism of action on TFPI and anti-FXa levels, additional safety data at this dose is warranted. As discussed in Section 6.1.11 below, efficacy was demonstrated with the low dose of Andexxa so a higher dose may not be needed for patients experiencing bleeding within the therapeutic range studied and requiring reversal of apixaban; this study does not inform on the efficacy for bleeds associated with supratherapeutic levels of the anticoagulant/anti-FXa activity.

6.1.5 Directions for Use

The draft label includes illustrated reconstitution instructions.

Andexxa was supplied as a single-use (b) (4) with lyophilized powder for administration by intravenous (IV) injection after reconstitution with Sterile Water for Injection. The reconstituted solution was given as a bolus (Part 1; target rate of approximately 30 mg/minute) immediately followed by a continuous IV infusion for up to 120 minutes.

A lyophilized product containing all ingredients in the active product and with the same appearance and container closure and was used for the placebo.

6.1.6 Sites and Centers

Celerion
2420 West Baseline Road
Tempe, Arizona 85283
United States

6.1.7 Surveillance/Monitoring

An Independent Safety Committee reviewed unblinded safety data from Part 1 prior to proceeding with Part 2. No modifications of dose or regimen were made for Part 2.

See Appendix II for the complete schedule of assessments.

Safety assessments included adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and laboratory assessments (hematology, biochemistry, coagulation markers). Specifically (b) (4), prothrombin fragment 1+2, D-dimer was assessed. Additional plasma samples were collected at select time points to allow for

future performance of additional assays of the coagulation system (e.g., Russell's Viper Venom Time, thrombin-antithrombin, fibrinogen, ATIII, total and free TFPI) based upon the results from the other PD assays and the safety profile of Andexxa. Clinical screening for thrombosis was done using the Wells score for DVT and PE at baseline and post-infusion (Day 4, 5, Day 8/discharge, Day 15, 36 and 43).

Per the applicant, anti-Andexxa, anti-FX, and anti-FXa, antibodies were evaluated using an electrochemiluminescence based assay. For any sample that was positive for antibodies against Andexxa, the potential for neutralizing antibody activity was to have been further assessed by measuring the functional activity of Andexxa in plasma. However, as discussed in section 4.2, the immunogenicity program was inadequate because Portola did not test for neutralizing antibodies against FX and FXa.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint

In Part 1, the primary endpoint was percent change from baseline in anti-FXa activity at the nadir, when nadir was defined as the smaller value for anti-FXa activity at the +2 minutes or +5 minutes time point following the end of the bolus.

In Part 2, the primary endpoint was the percent change from baseline in anti-FXa activity from baseline to nadir, when nadir was defined as the smaller value for anti-FXa activity between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion.

The baseline for the primary endpoint in both parts was the anti-FXa activity just prior to administration of Andexxa/placebo, 3 hours following the Day 4 dose of apixaban.

Secondary Endpoints

Part 1

- The occurrence of ≥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 as the smaller value for free apixaban concentration at the +2 minute or +5 minute time point after the completion of the Andexxa bolus.
- The change in thrombin generation and the occurrence of thrombin generation above the lower limit

Part 2

- The percent change from baseline in anti-FXa activity at its nadir, where nadir is defined as the smallest value for anti-FXa activity at the +2 minute or +5 minute time point after the completion of the Andexxa bolus.
- The occurrence of ≥80% reduction in anti-FXa activity from its baseline to nadir, where nadir is defined as the smallest value for anti-FXa activity between the

110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

- The change from baseline in free apixaban concentration (ng/ml) at its nadir, where nadir is defined as the smallest value for free apixaban between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- The occurrence of thrombin generation above the lower limit of the normal range at its peak, where peak is defined as the largest value for anti-FXa activity between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

Reviewer Comment: The applicant states that anti-FXa activity was chosen as the primary (surrogate) endpoint because "it is a direct measurement of inhibition of the target enzyme FXa by the inhibitors and a biomarker of reversal of anticoagulant activity that is considered reasonably likely to predict clinical benefit," as evidenced by data that show that plasma concentration of the FXa inhibitor correlate with ex-vivo anti-FXa activity and that in animal models of blood loss a decrease in plasma-free fraction of FXa inhibitor and/or anti-FXa activity correlated with reduction in blood loss.

FDA agreed with Portola's proposal to use anti-FXa activity as an indicator of reversal of anticoagulation for direct FXa inhibitors because of the direct correlation of anti-FXa with drug (anticoagulant) levels and Andexxa's demonstrated ability to reduce drug levels. FDA advised that in order to convert from a possible accelerated approval to a standard approval, the confirmatory study would need to demonstrate a correlation between reduction of anti-FXa activity and improved clinical outcomes. However, because anti-FXa has not been shown to correlate with improved bleeding outcomes in previous studies, FDA advised Portola to consider a clinical endpoint as the primary endpoint to support approval if correlation was not demonstrasted. FDA further advised that percent reduction in anti-FXa activity was not considered a clinically relevant primary endpoint, because a statistically significant reduction in anti-FXa activity could result in nadir anti-FXa activity levels that were still in the therapeutic range. FDA acknowledged that the degree of reversal of anti-FXa activity required to impact bleeding is unknown, and advised Portola to use all available data to propose a target anti-FXa level that would be associated with an acceptable risk of bleeding. Portola proposed a level of 30 ng/mL based on published recommendations from a working group on perioperative hemostasis (Pernod, *et al*.). FDA did not consider this proposed threshold level to be acceptable because 1) the level was not established based on pre-clinical or clinical data; it was derived from assumptions of plasma concentrations based on half-life, Cmax, normal renal clearance and interval

between dose and surgery and bleeding experience and 2) there were no data submitted to support that this threshold level would predict for an acceptable risk of bleeding.

Additionally, although direct FXa inhibitors do not require routine monitoring of the anticoagulant effect, it is evident that emergency situations may necessitate assessment of coagulation status. Currently, the relationship between test results and bleeding is unknown as there is a lack of outcomes data in bleeding patients; therefore the clinical value of coagulation test results is limited. FDA advised Portola to consider developing a companion diagnostic that would aid physicians in determining if additional dosing of Andexxa was required based on nadir (post-dosing) anti-FXa levels. Portola responded that it would not pursue a companion diagnostic at this time.

FDA did not accept the surrogate endpoint of anti-FXa activity levels for enoxaparin because low molecular weight heparins, such as enoxaparin, have a dual mechanism of inhibiting FXa and FIIa (thrombin). This issue was communicated to Portola in the filing communication letter of 16 February 2016, highlighted in the mid cycle communication on 13 April 2016, noted in an email from FDA to Portola on 18 July 2016 and discussed during the internal meeting with FDA on 27 July 2016.

6.1.9 Statistical Considerations & Statistical Analysis Plan

For both Part 1 and Part 2, the primary efficacy analysis compared the primary endpoint between the 2 treatment groups. The comparison was conducted using an exact Wilcoxon rank sum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level. For both Part 1 and Part 2, the secondary efficacy analyses consisted of comparing the secondary endpoints between the two treatment groups. The dichotomous secondary endpoints were compared between treatment groups using Fisher's Exact Test. The secondary endpoints were defined as change from baseline (continuous measure) and compared between treatment groups using an exact Wilcoxon rank-sum test. In general, continuous variables were summarized by descriptive statistics.

Subjects who were not evaluable due to missing value(s) related to study drug were not to be replaced. For the endpoints that were defined as percent change from baseline, the subject's imputed value was 0% (i.e., using the baseline value as the nadir value). For the dichotomous endpoints, the subject's outcome was considered as a treatment failure.

6.1.10 Study Population and Disposition

A total of 68 subjects were enrolled and received apixaban (34 in Part 1 and 34 in Part 2). Of these, 66 subjects were randomized (34 subjects in Part 1 [25 Andexxa, 9 placebo] and 32 in Part 2 [24 Andexxa, 8 placebo]).

In part 1, 33 of the 34 randomized subjects completed the study. One subject ((b) (6)) randomized to the Andexxa group did not receive study drug.

In part 2, all 32 randomized subjects completed the study. One subject ((b) (6)) randomized to the Andexxa group was not included in the Efficacy Analysis 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.

6.1.10.1 Populations Enrolled/Analyzed

Safety Analysis Population- all subjects randomized and treated with study medication (Andexxa or placebo); n=33 for part 1 and 32 for part 2.

Efficacy Analysis Population (modified intent to treat; mITT) - all randomized subjects who received any amount of study drug treatment and have baseline value for anti-FXa and at least one of the following time points: +2 minute or +5 minute time point after the end of the bolus (part 1) or all randomized subjects who received any amount of study drug treatment and have baseline for anti-FXa and at least one of the following time points: 110-minute time point during the continuous infusion, -2 minute time point during the continuous infusion, or +5 minute time point after the end of the continuous infusion (part 2). The subjects in the Safety and Efficacy Analysis (mITT) were identical; n=33 for part 1 and 31 for part 2.

The Per-protocol (PP) Population consisted of all mITT subjects who received the full dose of medication administered as prescribed; n=33 for part 1 and 31 for part 2.

6.1.10.1.1 Demographics

Of the 65 subjects included in the safety database, most were male (41/65; 63%), white (62/65; 95%), not Hispanic or Latino (38/65; 58%), with a mean age of approximately 60 years.

Table 8: Demographic and Baseline Characteristics (Safety Analysis Population)

Demographic or Baseline Parameter	Part 1			Part 2		
	Andexanet (N = 24)	Placebo (N = 9)	Total (N = 33)	Andexanet (N = 24)	Placebo (N = 8)	Total (N = 32)
Age, years						
Mean ± SD	61.0 (6.37)	59.0 (3.54)	60.4 (5.75)	59.4 (7.83)	59.5 (6.91)	59.4 (7.50)
Median (range)	60.0 (50, 73)	58.0 (55, 66)	59.0 (50, 73)	56.0 (50, 73)	58.5 (52, 70)	56.5 50, 73
Gender, n (%)						
Male	13 (54.2)	6 (66.7)	19 (57.6)	17 (70.8)	5 (62.5)	22 (68.8)
Female	11 (45.8)	3 (33.3)	14 (42.4)	7 (29.2)	3 (37.5)	10 (31.3)
Ethnicity, n (%)						
Hispanic or Latino	10 (41.7)	4 (44.4)	14 (42.4)	11 (45.8)	2 (25.0)	13 (40.6)
Non-Hispanic or Latino	14 (58.3)	5 (55.6)	19 (57.6)	13 (54.2)	6 (75.0)	19 (59.4)
Race, n (%)						
White	24 (100.0)	9 (100.0)	33 (100.0)	21 (87.5)	8 (100.0)	29 (90.6)
Black or African-American	0	0	0	2 (8.3)	0	2 (6.3)
Asian	0	0	0	1 (4.2)	0	1 (3.1)
Other	0	0	0	0	0	0
Body Mass Index, kg/m^2						
Mean ± SD	26.647 (2.5130)	27.407 (2.5031)	26.854 (2.4946)	27.445 (2.0803)	27.794 (2.3742)	27.533 (2.1230)
Median (range)	26.540 (22.76, 31.76)	27.200 (24.07, 31.19)	26.620 (22.76, 31.76)	27.405 (22.44, 31.13)	26.895 (25.18, 31.26)	27.405 22.44, 31.26

SD = standard deviation.

Source: CSR 14-503, page 63/141.

Reviewer Comment: The study population is adequate to demonstrate the ability of Andexxa to reverse anti-FXa levels, and is representative of the older population that is likely to use this product. However, as noted previously, the exclusion of patients with renal insufficiency and those with increased risk of thrombosis precludes this population from adequately representing the broader population targeted by the proposed indication. Additional data in the target population is needed to fully assess the safety and efficacy of this product. Although there are gender, race and ethnicity imbalances, there is no expectation of different efficacy based on these baseline characteristics.

6.1.10.1.3 Subject Disposition

As discussed in Section 6.1.10 above, 68 subjects (34 subjects in each arm) were enrolled in the study and received apixaban. A total of 66 (97%) of the enrolled subjects were randomized, including 34 randomized in part 1 (25 Andexxa; 9 placebo) and 32 randomized in part 2 (24 Andexxa; 8 placebo). The 3:1 randomization scheme was maintained.

Of the 34 randomized in Part 1, 33 received study drug and completed the study. All 33 subjects were included in the SAP, mITT and PP analyses.

- Subject (b) (6) was a 59 year-old, White female who was randomized to Andexxa but did not receive study drug "due to an IV access issue" and therefore was not included in the safety or efficacy analyses.

All 32 subjects randomized in Part 2 completed the study; however, one subject randomized to the Andexxa group was not included in the Efficacy Analysis (mITT) or PP Populations because study drug was discontinued before the infusion was completed and the site did not collect follow-up blood tests on that day:

- Subject (b) (6) was a 51 year-old Asian male with a medical history significant for hives who received 53.9 mL of the planned 88 mL of Andexxa because the study drug was discontinued after the subject experienced a nonserious, mild AE of infusion reaction. Within one hour of the bolus dosing, the subject had generalized erythematous hives and sinus tachycardia that was consider by the Investigator to be related to the study drug. The subject also experienced erythema distal to the infusion site that was considered unrelated to the study drug. The infusion was discontinued and the subject received a single dose of oral diphenhydramine.

Reviewer Comment: The number of subjects who were discontinued and the reasons for their discontinuation does not undermine the data or the conclusions drawn about the clinical trial.

6.1.11 Efficacy Analyses

The study won on all primary and secondary efficacy endpoints: significant differences in anti-FXa activity reduction, free apixaban concentration and restoration of thrombin generation were observed between subjects in the Andexxa and placebo groups.

6.1.11.1 Analyses of Primary Endpoint(s)

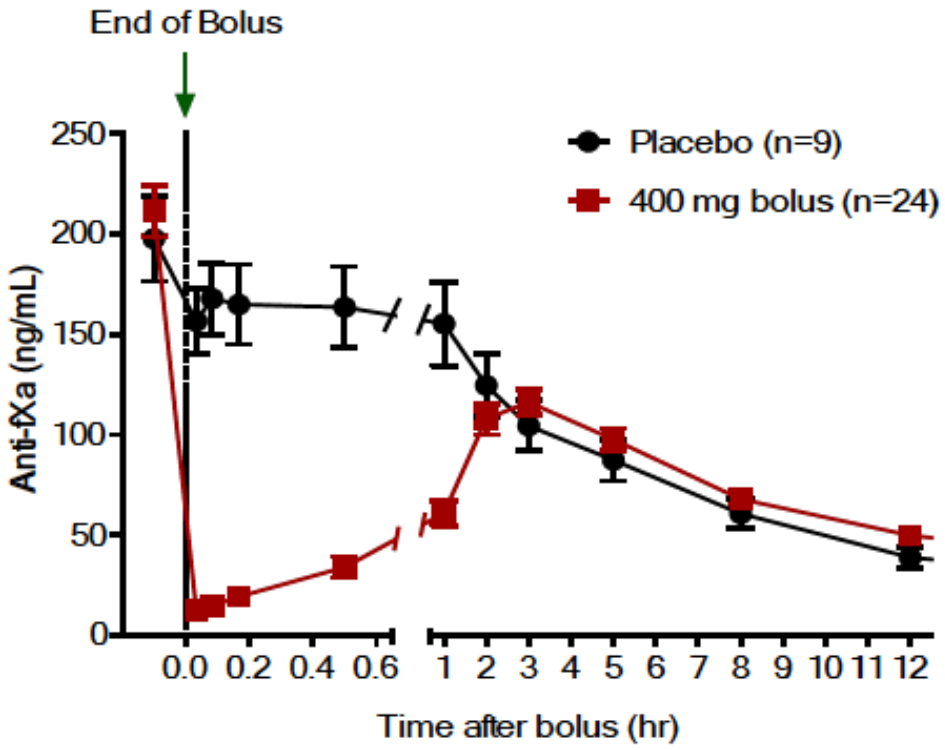
The primary efficacy analysis compared the primary endpoint of percent change from baseline in anti-FXa activity at the nadir between the two treatment groups using an exact Wilcoxon ranksum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level. The primary efficacy analyses for Part 1 and Part 2 were done using the Efficacy Analysis (mITT) Population, which was comprised of subjects who received any amount of study drug and had baseline value for anti-FXa and ≥1 of the following time points: +2 minute or +5 minute time point after the end of the bolus (Part 1; n=33/34) or 110-minute time point during the continuous infusion, -2 minute time point during the continuous infusion, or +5 minute time point after the end of the continuous infusion (Part 2; n=31/32).

<u>Part 1</u>

The mean (SD) anti-FXa activity levels after anticoagulation with apixaban (baseline) were 211.3 ng/mL (62) and 197.6 ng/mL (63.2) for the Andexxa and control groups, respectively. Nadir levels (SD) of anti-FXa were lowest two minutes after the bolus infusion at 12.5 ng/mL (3.4).

The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -93.9% (1.6%) for the Andexxa group and -20.7% (8.6%) for the placebo group (p<0.0001). Anti-FXa returned to levels observed in the placebo group (or higher) within 180 minutes after the end of the bolus.

Figure 3: Anti-FXa Activity following Andexxa Bolus or Placebo (Part 1)



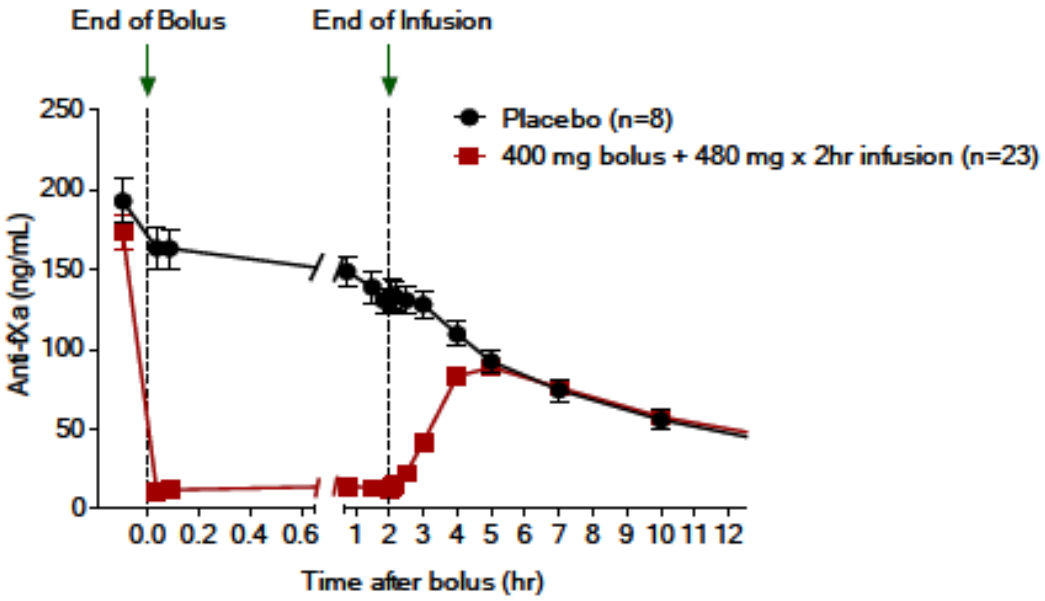
Source: CSR 14-503, page 68/141.

Part 2

The mean (SD) anti-FXa activity levels after anticoagulation with apixaban were 173 ng/mL (50.5) and 191.7 ng/mL (34.3) for the Andexxa and control groups, respectively. Nadir levels of anti-FXa were lowest two minutes after the bolus infusion at 10.9 ng/mL (2.3).

The mean percent change from baseline in anti-fXa activity at the nadir was -92.3% (±2.8%) for the Andexxa group and -32.7% (±5.6%) for the placebo group (p<0.0001). Anti-FXa returned to levels observed in the placebo group within 300 minutes after the end of the bolus or bolus plus infusion.

Figure 4: Anti-FXa Activity following Andexxa Bolus + Infusion or Placebo (Part 2)



Source: CSR 14-503, page 70/141.

Reviewer Comment: The observed steady state drug concentrations in this study are comparable to concentrations observed in the phase 3 studies used to support licensure of apixaban. Therefore these results would be generalizable to the target population for which bleeding is observed within the same therapeutic range. However, an important limitation of this database is that although bleeding is reported within therapeutic range, patients will be expected to bleed with supratherapeutic levels of anticoagulant; this study does not inform on the safety and efficacy of reversal in that setting.

These data demonstrate that Andexxa does not result in complete reversal of anticoagulation, which questions the suitability of anti-FXa activity as a surrogate. The clinical significance of nadir levels of <12.5 ng/mL is unknown as it remains unclear whether complete reversal is required to see improved clinical outcomes in bleeding patients. Although the observed depth of reversal may be adequate as nadir levels are below the levels expected after withdrawal of anticoagulation for 48 hours based on the report by Pernod *et al*, in the phase 2 clinical trial of Andexxa, nadir anti-FXa levels were approximately three to four times higher than those observed in the placebo group at 48 hours post-dose (see Table 5 of the CDER clinical pharmacology consult). These findings further reinforce the need to identify target levels that predict for hemostasis. In the Midcycle Communication, FDA advised Portola of these concerns and Portola countered that 'animal models (rat tail transection model with enoxaparin-anticoagulated animals) showed near-complete reversal of bleeding with just a 50% decrease in anti-FXa activity to a level (~2.5 IU/mL) that was still a supra-therapeutic and that rabbit liver laceration models with rivaroxaban and edoxaban showed restoration of hemostasis with only partial lowering of anti-FXa activity (to levels well above the no effect level)', that in patients with hemophilia only 50-60% restoration of normal levels is required to stop bleeding, and that data from the confirmatory study show that normalization

of thrombin generation and successful hemostatis was achieved for subjects with supratherapeutic levels of apixaban or rivaroxaban. The use of thrombin generation as a surrogate of the reduction of anti-FXa activity, which is being used as a surrogate of clinical benefit, was not an acceptable approach to review this application under accelerated approval.

The data also suggest that duration of effect (as evidenced by reduction in anti-FXa) may not be sufficient for bleeding events that require prolonged reversal, such as ICH where morbidity and mortality from anticoagulation-related bleeding is high. As noted above, a rebound in anti-FXa activity was noted within 180 (Part 1) or 300 (Part 2) minutes after the bolus. The exact mechanism for the rebound is unknown. Prior to BLA filing, FDA advised Portola that this rebound issue was of concern and that a 2-hour infusion may not be a clinically meaningful duration for reversal; this was reiterated in the Midcycle Communication. FDA further advised that additional dosing regimens (e.g., longer infusion and/or repeat dosing) should be evaluated to address this concern. Portola countered with the following arguments: 1) based on the kinetics of clotting, a definitive hemostatic plug can form within a minute or two and that a stable clot can form within minutes if not impeded by an anticoagulant making it theoretically possible to achieve hemostasis within minutes; with Andexxa's quick action to reverse FXa inhibition, the proposed dosing regimen may be sufficient; 2) animal data show that a single bolus of Andexxa can result in rapid and near-complete hemostasis; 3) thrombin generation data is restored and remains in the normal range for >20 hours and 4) preliminary data from the ongoing confirmatory study demonstrates efficacy with this dose. FDA considered Portola's claims; however, in the absence of acceptable data in the BLA submission to support claims of clot stability and the purported kinetics of clotting, FDA remains unconvinced that the abbreviated duration of reversal is adequate to control hemostasis where prolonged duration of reversal may be necessary. Advice obtained through consult opinions suggested the need for sustained reversal for ICH. With regard to adequacy of animal data and restoration of thrombin generation and its contribution to hemostasis, the conclusions drawn from the CMC review memo was that neither the animal models nor the *ex vivo* thrombin generation can be used to predict effect of treatment in humans: 1) there is no data to establish the correlation between the models of injury in small animals and the extent of bleeding and hemostasis in humans, particularly in clinically relevant bleeding events in elderly patients on the anti-FXa therapy; 2) although Portola found that the sustained normalization of thrombin generation in Phase 2 and 3 trials was due to the anti-TFPI action of Andexxa, Portola has not provided evidence that Andexxa can interact with animal TFPI or cause elevation of thrombin generation through this mechanism in animals; 3) Portola used two different versions of the thrombin generation assay for Phase 2 and Phase 3 studies, but failed to properly qualify either of these analytical methods for the combined effects of FXa inhibitors and Andexxa and to bridge these two methods with each other or the previously published thrombin generation studies in humans. Portola has not provided data to support the threshold levels of thrombin generation that correlate with control of bleeding; therefore thrombin generation data were not used to support Portola's

assertion that the duration of effect is sustained. Portola committed to evaluating thrombin generation and additional dosing regimens in future studies. Please also refer to reviewer comments in 6.1.11.2.

6.1.11.2 Analyses of Secondary Endpoints

Note: Baseline for assessments of anti-FXa activity and free Apixaban concentration is defined as the measurement obtained at 3-hour time point after the apixaban dose on Study Day 4. Baseline for the evlaution of ETP is defined as Day 1 prior to any anticoagulant administration.

Occurrence of ≥80% Reduction in Anti-FXa Activity from its Baseline to Nadir:
For both parts, all subjects in the Andexxa group had ≥80% reduction in anti-FXa activity.

Change From Baseline in Free Apixaban Concentration at Nadir
In Part 1, mean unbound levels of apixaban decreased significantly from baseline levels of 11.1 ng/mL (3.3) to a nadir of 1.8 ng/mL (0.6) and returned to levels observed in the placebo group (or higher) within 120 minutes after the end of the bolus. This decrease was significantly higher in subjects who received Andexxa than in subjects who received placebo ($p<0.01$).

In Part 2, mean unbound levels of apixaban decreased significantly from baseline levels of 7.9 ng/mL (2.8) to a nadir of 1.4 ng/mL (0.4) and returned to levels observed in the placebo group within 240 minutes after the end of the bolus. This decrease was significantly higher in subjects who received Andexxa than in subjects who received placebo ($p<0.01$).

Change in ETP from Baseline to its Peak
ETP from baseline to its peak increased significantly more in subjects who received Andexxa than in subjects who received placebo ($p<0.0001$), in both Part 1 and Part 2.

Note: For ETP, the normal range was defined as the mean of the Day 1 pre-apixaban value from all subjects ±1 SD.

In Part 1, mean ETP increased from a baseline of 554.8±157.8 nmol/min to a peak of 1825.29±362 nmol/min. Thrombin generation became similar to placebo at approximately 22 hours post-bolus.

In Part 2, mean ETP increased from a baseline of 590.9±174.3 nmol/min) to a peak of 1780.4±324.2 nmol/min). Thrombin generation became similar to placebo at >20 hours post-infusion.

In the placebo arm, thrombin generation was not restored until 8 to 10 hours after the bolus, which is consistent with the timeframe for the clearance of unbound apixaban.

Reviewer Comment: As discussed above, coagulation tests represent surrogate outcomes that may not reflect clinical efficacy in the context of bleeding. Without data to support that normalization of thrombin generation is necessary to form stable clots, interpretation of these thrombin generation data is problematic; it is unclear to what degree the levels seen in the placebo arm at various time points could result in hemostasis. Furthermore, Dr. Ovanesov has advised that additional studies to characterize the PD of TFPI inhibition and its relation to the thrombin generation assay are needed to fully understand the significance of these findings. As such, the desired extent of reversal of anti-FXa activity needed for hemostasis cannot be estimated based on normalization of thrombin generation.

6.1.11.3 Subpopulation Analyses

Due to the size of this individual trial, no inferential subgroup analyses were performed.

6.1.11.4 Dropouts and/or Discontinuations

No subjects discontinued early from the study. One subject ((b) (6)) was not evaluable for the efficacy analysis due to missing data after being withdrawn prematurely from study drug treatment (see Section 6.1.10.1.3).

6.1.11.5 Exploratory and Post Hoc Analyses

The following PD markers were analyzed: (b) (4) .

In Part 1 and Part 2, apixaban increased (b) (4) during the 3.5 day treatment, which was followed by a more rapid decrease in the mean (b) (4) following Andexxa dosing vs. placebo dosing from Day 4, 2 minutes post-bolus until Day 5.

In Part 1 and Part 2, (b) (4) values were similar between the Andexxa and placebo group and did not change over time compared to baseline.

Reviewer Comment: As with (b) (4) tests represent outcomes that may not reflect clinical efficacy in the context of bleeding. Furthermore, none of these PD markers are used to monitor for anticoagulation with direct Fxa inhibitors, so the interpretation and the usefulness of these results are limited.

6.1.12 Safety Analyses

6.1.12.1 Methods

Adverse events (AEs) were coded by using Medical Dictionary for Regulatory Activities (MedDRA), Version 16.1 and are analyzed based on the principle of treatment emergence on or after first infusion with the trial drug. The Safety Analysis Population consisted of all subjects randomized and treated with study drug (Andexxa or placebo). Causality (unrelated, unlikely, possible, and probable) was assessed by the investigator.

6.1.12.2 Overview of Adverse Events

Exposure to Andexxa

Per Table 11 of the CSR, 24 subjects in Part 1 received a single IV bolus of Andexxa, and 9 subjects received a single IV bolus of placebo, as per protocol.

In part 2, 30/32 subjects received the full dose of Andexxa or placebo:

- Subject (b) (6) received a total of 53.9 mL instead of 88 mL of Andexxa because the subject experienced an AE of hives.
- Subject (b) (6) received a total of 87 mL instead of 88 mL of placebo because the infusion was interrupted secondary to an AE of infusion reaction (nausea, dizziness and generalized sensation of warmth). The infusion was subsequently restarted but the complete dose was not given.

Treatment Emergent Adverse Events

Overall, treatment-emergent AEs, herein after referred to as AEs, occurred in 29/65 (44.6%) subjects, including 19/48 (39.6%) treated with Andexxa and 10/17 (58.8%) treated in the placebo group.

Table 9: Overview of Adverse Events (Safety Analysis Population)

Category Subjects With ≥1 AE	Part 1 (n=34)		Part 2 (n=32)	
	Andexxa (n=25) n (%)	Placebo (n=9) n (%)	Andexxa (n=24) n (%)	Placebo (n=8) n (%)
All TEAEs	9 (37.5)	6 (66.7)	10 (41.7)	4 (50)
AEs within the first hour of study drug exposure	4 (16.7)	1 (11.1)	4 (16.7)	2 (25)
TEAEs related to study drug	4 (16.7)	0	7 (29.2)	2 (25)
SAEs	0	0	0	0
AEs of special interest[a]	0	0	0	0
Premature discontinuation of study drug due to AE	0	0	1 (4.2)	0
Withdrawals from study due to AE	0	0	0	0
Deaths	0	0	0	0

AEs = adverse events; SAE = serious AEs; TEAE = treatment-emergent AE.
[a] = AE of special interest were VTE of any severity, moderate or severe infusion reaction, AST, or ALT >3×ULN if associated with a total bilirubin >2×ULN, or AST or ALT >3×ULN or total bilirubin >2×ULN if associated with clinical signs or symptoms of liver injury (eg, jaundice).
Source: Adapted from CSR 14-503, page 92/141.

Specifically, AEs were reported in 15 subjects in Part 1, including 9/24 (37.5%) in the Andexxa group and 6/9 (66.7%) in the placebo group. The most common (>10%) reported AE was infusion-related reaction, headache, and dermatitis contact in the Andexxa group. The only AE that occurred with a >10% differences between the Andexxa and placebo groups in Part 1 was infusion-related reaction. No subject experienced a moderate or severe AE in the Andexxa group.

A total of 14 subjects reported AEs in Part 2, including 10 (41.7%) in the Andexxa group and 4 (50%) in the placebo group. The most common (>10%) reported AE was vessel puncture site hemorrhage and infusion-related reaction in the Andexxa group. The only AE that occurred with a >10% differences between the Andexxa and placebo groups in

Part 2 was vessel puncture site hemorrhage. Two subjects in the Andexxa group experienced moderate AEs of myalgia and pain in the extremity; however, no subject had a severe AE.

Of the subjects treated with Andexxa in Part 1, 4 (16.7%) experienced a total of 7 related AEs of infusion-related reactions (n=3), muscle spasms (n=1), pain in extremity (n=1), dizziness (n=1) and headache (n=1).

In Part 2, 7 subjects (29.2%) experienced 10 related AEs of abdominal distension (n=1), constipation (n=2), flatulence (n=1), infusion site pain (n=1), vessel puncture site hemorrhage (n=1), and infusion-related reaction (n=4).

Reviewer Comment: Overall, Andexxa appears well tolerated. AEs were mostly mild and resolved without sequelae, including infusion-related reactions.

6.1.12.3 Deaths

There were no deaths.

6.1.12.4 Nonfatal Serious Adverse Events

There were no serious adverse events (SAEs).

6.1.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events (TE):
No confirmed thromboembolic events were reported; however, elevations in at least one of the thrombogenic markers measured (d-dimer, prothrombin fragments 1+2) was noted in subjects dosed with Andexxa in both parts of the study (see 6.1.12.6 below).

Reviewer Comment: The safety monitoring was adequate to identify clinically meaningful thrombotic events, as patients were screened routinely using the Wells Score. The fact that no healthy volunteer subjects developed a TE does not mean that Andexxa anti-TFPI mechanism of action is not associated with increased risk of thrombosis because the safety database from this trial may not be large enough to capture these events. As mentioned previously, clinically meaningful conclusions about the risk for thrombosis in the target population cannot be determined from these studies.

Immunogenicity
The applicant states that "antibody testing was performed for anti-andexanet, anti-FX, and anti-FXa antibodies and neutralizing antibody anti-FXa activity with apixaban and with apixaban plus andexanet."

In Part 1, 3 subjects had anti-andexanet antibodies; none were associated with any adverse events or lack of efficacy:

- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (1:80 titer).

- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 15 (1:160 titer) and at OPV Day 43 (1:80 titer).
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (1:40 titer).

In Part 2, 7 subjects had anti-andexanet antibodies:
Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (titer 1:10).

- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (titer 1:20).
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (titer 1:10).
- Subject (b) (6) had anti-andexanet antibodies detected at INPT Day 1 (1:10), OPV Day 15 (1:40), OPV Day 36 (1:40), and OPV Day 43 (titer 1:40).
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 43 (titer 1:10).
- Subject (b) (6) had anti-andexanet antibodies detected at INPT Day 1 (titer 1:10), INPT Day 15 (titer 1:2560), INPT Day 36 (titer 1:320), and OPV Day 43 (titer 1:160).
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 15 (titer 1:10).

Reviewer Comment: Portola has not developed assays to detect anti-drug antibodies (ADAs) that may neutralize endogenous coagulation Factors X and Xa. Although the risk of cross-reacting antibodies to native FX may be low given the limited duration of treatment with Andexxa (single dose), the development of such an antibody would result in an acquired FX deficiency and an increased risk for recurrent mucosal hemorrhages (e.g. recurrent epistaxis, hematuria, gastrointestinal bleeding), hemarthroses, intracranial and soft tissue hemorrhages, and menorrhagia. Portola plans to address this in future studies.

Hypersensitivity/Allergic Reactions
Infusion reactions were captured as "infusion reaction – XX" with XX being the AE experienced by the subject. Each AE was coded to "Infusion-related reaction" using MedDRA. An event occurring during or shortly after the bolus or infusion was to be labeled as an "infusion-related reaction—specific sign or symptom" unless the investigator judged that the event was unrelated to study drug administration.

In Part 1, 3 subjects (12.5%) in the Andexxa group and no subjects in the placebo group had infusion-related reactions. In Part 2, 4 subjects (16.7%) in the Andexxa group and 2 subjects (25.0%) in the placebo group had infusion-related reactions. All were mild in severity, considered by the Investigator to be related to study drug, and resolved:

<u>Subjects in the Andexxa Group:</u>

- Subject (b) (6) had 3 AEs of mild infusion-related reaction (flushing, face edema, ocular hyperemia) considered unrelated to apixaban but related to study drug. No action was taken and the AEs resolved.
- Subject (b) (6) had 4 AEs of mild infusion-related reaction (flushing, feeling hot, parosmia, dysgeusia) considered unrelated to apixaban but related to study drug. No action was taken, and the AEs resolved.

- Subject (b) (6) had 2 AEs of mild infusion-related reaction (dysgeusia, sinus pressure) considered unrelated to apixaban and related to study drug. No action was taken, and the AEs resolved.
- Subject (b) (6) had 4 AEs of mild infusion-related reaction (flushing, feeling hot) occurring simultaneously, all considered unrelated to apixaban and related to study drug. No action was taken, and the AEs resolved.
- Subject (b) (6) had 2 AEs of mild infusion-related reaction (urticaria, sinus tachycardia) considered related to study drug. See Section 6.1.10.1.3.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (chest discomfort) considered related to study drug. No action was taken, and the AE resolved.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (dysgeusia) considered related to study drug. No action was taken, and the AE resolved

Subjects in the Placebo Group

- Subject (b) (6) had 3 AEs of mild infusion-related reaction (dizziness, nausea, feeling hot) deemed related to study drug. The infusion was interrupted and restarted (but not completed), and the AEs resolved.
- Subject (b) (6) had 2 AEs of mild infusion-related reaction (papular rash, lacrimation increased), both deemed unrelated to apixaban and related to study drug. No action was taken, and the AEs resolved.

The only infusion-related reaction symptoms that occurred in >1 subject were dysgeusia (2 subjects in Part 1 and 1 subject in Part 2) and flushing (2 subjects each in Part 1 and Part 2).

Reviewer Comment: The product appears well tolerated. No significant differences in infusion-related reactions were noted. The assessments of causality in each case were appropriate.

6.1.12.6 Significant Clinical Test Results

Coagulation Tests

Elevations in markers of coagulation (D-dimer and prothrombin fragment 1+2) were observed in patients receiving Andexxa in Part 1 and 2 of the study. Three subjects ((b) (6)) had significantly prolonged elevations of either D-dimer or F1+2 levels for 11 days that started immediately following treatment with Andexxa. These elevations were not associated with clinical evidence of thrombosis.

Part 1

Ten (42%) subjects in the Andexxa group and no subject in the placebo group had a D-Dimer that was greater than twice the upper limit of normal (ULN) at ≥1 time point. These elevations were noted as far out as Day 43 for at least 2 subjects:

- Subject (b) (6) had elevated D-Dimer values on Day 1, prior to apixaban and Andexxa /placebo, and remained elevated throughout the study.
- Subject (b) (6) had D-Dimer elevations >2×ULN on Days 15, 36, and 43, with levels ≤2×ULN on Days 4 to 8.

Eighteen (75%) subjects in the Andexxa group and no subjects in the placebo group had F1+2 that was >2×ULN at ≥1 time point. These elevations were noted as far out as Day 6 for at least 2 subjects:

- Subject (b) (6) had F1+F2 elevations >2×ULN on Days 4 to 6, with levels ≤2×ULN on Days 7, 8, 15, 36, and 43.
- Subject (b) (6) had F1+F2 elevations >2×ULN on Days 4 to 6, with levels ≤2×ULN on Days 7, 8, 15, and 43.

Part 2

Ten (42%) subjects in the Andexxa group and no subjects in the placebo group also had a D-Dimer that was >2×ULN at ≥1 time point. These elevations were noted as far out as Day 36 for at least 1 subject:

- Subject (b) (6) had D-Dimer elevations >2×ULN on Day 36, with levels ≤2×ULN on Days 4 to 8, 15, and 43.

A total of 23 (96%) subjects in the Andexxa group and no subjects in the placebo group had F1+2 that was >2×ULN at ≥1 time point. The latest time point of a F1+2 elevation >ULN was to Day 15 and occurred in 1 subject:

- Subject (b) (6) had F1+2 elevations >2×ULN on Days 4, 5, and 15, with levels ≤2×ULN on Days 6 to 8, 36, and 43.

As noted above none of these elevations were associated with clinical evidence of thrombosis.

Reviewer Comment: These elevations are consistent with activation of the coagulation system and provide some evidence of the potential procoagulant properties of Andexxa. However, in the absence of thrombosis, the clinical significance of these findings remains unclear. Additional data in the target population is needed to fully assess any associated product-related risk of thrombosis. In the absence of published data, a more precise understanding of whether Andexxa may be associated with increased clinical thrombotic and other risks requires a control population.

<u>12-lead Electrocardiograms</u>

Standard 12-lead electrocardiograms were recorded electronically at pre-specified time points, including screening, baseline after anticoagulant dosing but prior to Andexxa, discharge, and outpatient follow-up. New post-baseline PR intervals > 200 msec were observed in more than one subject, and an additional subject was noted to have a QTcF change from baseline > 60 msec. All of these events occurred with bolus dosing only.

- Subject (b) (6) reportedly had a normal PR interval prior to Andexxa (baseline Inpatient Day 4 pre-dose value 192 msec); PR interval recorded to be 210 sec at discharge (Day 8) and 202 msec at the outpatient follow-up visit (Day 43). (Note: pre-dose value close to 200 msec).
- Subject (b) (6) had a baseline Inpatient Day 4 pre-dose PR interval of 208 msec; Inpatient Day 4, 5 minutes post-bolus PR 204 msec, Discharge Day (Day 8) PR 210 msec and Day 43 PR 210 msec. (Note: PR interval prolonged at baseline)

- Subject (b) (6) had a baseline Inpatient Day 4 pre-dose PR 208 msec and Discharge Day 8 PR 204 msec. (Note: prolonged PR interval pre-dose).
- Subject (b) (6) in the Andexxa group had PR intervals >200 msec at Baseline INPT Day 4 predose (208 msec), INPT Day 4, 5 minutes postbolus (204 msec), Discharge Day 8 (206 msec) and OPV Day 43 (204 msec).
- Subject (b) (6) had baseline Inpatient Day 4 pre-dose PR 214 msec, Inpatient Day 4, 5 minutes post-bolus PR 214 msec, Discharge Day 8 PR 224 msec and OPV Day 43 PR 212 msec. (Note: prolonged PR interval pre-dose).

In addition, Subject (b) (6) with baseline QTcF 412 msec developed a recorded QTcF interval of 488 msec at Inpatient Day 4, five minutes post-bolus. A repeat ECG done 2 minutes later displayed the QT interval as 374 msec and QTcF 406 msec. After review of the ECG tracings, the applicant concluded that the prolonged QT was a result of misreading by the machine, "probably because the T-waves were very flat, so the end of the wave was somewhat hard to distinguish."

Reviewer Comment: To further evaluate the clinical significance of these findings, a DCRP consult was obtained. The DCRP consultant noted that "If Andexxa caused PR and/or QTc prolongation, one would expect a reversible increase in the PR interval (and/or QTc interval, respectively) that temporally followed and correlated with Andexxa (or metabolite) exposure, with a return to baseline when the drug (or metabolite) is cleared." Furthermore, since Andexxa is cleared by Day 8, and there are no other apparent effects of Andexxa that, in turn, might cause PR prolongation (e.g., effects on metabolites that lead to ECG changes), a pattern of prolonged PR or borderline prolonged QTc at Days 13 and 48 is not suggestive of drug-associated PR prolongation. A review of the reported AEs did not identify other causes of PR prolongation, such as calcium channel-blockade and increase in vagal tone as evidenced by increased reports of bradycardia, constipation, or worsened reflux. To further evaluate if Andexxa has a clinically significant effect on PR or QT intervals, Portola was asked to revise the ongoing confirmatory study to include cardiac monitoring using standard 12-lead ECG; Portola responded that "Based on both the biology of the innate fXa molecule as well as the current data from the healthy volunteer studies, including the Phase 3 studies 14-503 and 14-504 in older subjects, there is no signal of effect on PR or QT intervals by andexanet. If the double-delta analysis suggests an effect not observed in the current review of the data, Portola will consider revising the ongoing ANNEXA-4 study (14-505) to include cardiac monitoring." In a follow-up email, Portola stated: "A placebo-subtracted mean change from baseline ("double delta") was performed on the Phase 3 data for studies 14-503 and 14-504, comparing the immediate pre-baseline ECG values to the post-bolus as well as the post-infusion timepoints. Two external cardiology consultants reviewed the data and came to similar conclusions that there was a lack of clinical effect by andexanet on the ECG parameters of QTc and PR."

Creatinine

No subject had evidence of acute kidney injury defined as increase in creatinine of ≥ 0.3 mg per dL (26.52 μmol per L) or ≥ 1.5-fold increase from baseline.

6.1.12.7 Dropouts and/or Discontinuations

See Section 6.1.11.4.

6.1.13 Study Summary and Conclusions

These results show that treatment with Andexxa results in a rapid reversal of anticoagulation that persists for the duration of the infusion; however depth of reversal is not sustained once the infusion is stopped.

The study won on all primary and secondary efficacy endpoints, demonstrating that treatment with Andexxa resulted in significant reductions in anti-FXa activity and free apixaban concentration, as well as restoration of thrombin generation. However, the apparent rebound that is observed once the infusion is complete suggests that a longer infusion or repeat dosing may be required to maintain a sustained reversal of anti-FXa activity levels.

Generalizability of the study to the target population is limited because renally impaired patients were excluded, as were patients with an increased baseline risk of thrombosis. The bleeding/re-bleeding risk and incidence of thrombosis may be different in these patients and therefore clinical outcomes may be different in this population. Furthermore, bleeding outcomes is also likely to be different in patients with supratherapeutic anticoagulant levels as nadir levels post-Andexxa are likely to remain in the therapeutic range; the depth of reversal may not be as robust which could result in continued bleeding or evidence of re-bleeding.

Andexxa appears to be reasonably well tolerated. The most common adverse reaction in the Andexxa group was infusion-related reactions. Most AEs were mild and no SAEs, thrombotic events, or deaths were reported. Overall, there were no clinically significant trends or safety concerns identified related to clinical test results. Elevations in coagulation markers were noted, but no subjects had a confirmed thromboembolic event.

6.1 Trial #2

14-503: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study In Older Subjects To Assess Safety And The Reversal Of Rivaroxaban Anticoagulation With Intravenously Administered Andexanet Alfa

6.2.1 Objectives (Primary, Secondary, etc)

Primary efficacy objective:
− To compare Andexxa and placebo with respect to reversal of rivaroxaban anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion.
• Secondary efficacy objectives:

− To compare reversal of rivaroxaban anticoagulation between Andexxa and placebo as measured by rivaroxaban free-fraction, both after a bolus and after a bolus followed by a continuous infusion.
− To compare reversal of rivaroxaban anticoagulation between Andexxa and placebo as measured by restoration of thrombin generation, both after a bolus and after a bolus followed by a continuous infusion.
• Safety objective:
− To assess the safety of Andexxa in subjects anticoagulated with rivaroxaban (ie, including bleeding events, thrombotic events, and immunogenicity), both after a bolus and after a bolus followed by a continuous infusion.

6.2.2 Design Overview

In the clinical development program for Andexxa, Trial 14-504 is the second of two trials that serves as the primary evidence to support safety and efficacy of Andexxa. This study was conducted as a randomized, double-blind, placebo-controlled study of older healthy subjects (ages 50–75 years) who were dosed to steady-state with rivaroxaban and then given Andexxa at the approximate steady-state maximum plasma concentration. Two dosing regimens of Andexxa were evaluated: bolus only (Part 1) and bolus followed by a continuous infusion (Part 2). Reversal of anticoagulation was evaluated by reduction in anti-FXa activity (primary efficacy endpoint), and reduction in unbound apixaban plasma levels and thrombin generation (secondary efficacy endpoints).

Eighty subjects were randomized 2:1 Andexxa:placebo, domiciled at the study site for 8 days, and subsequently followed for safety through Day 43. Subjects remained on study for approximately 8 to 12 weeks, depending on the length of screening. The study periods were as follows:
• Screening: Days -42 to -1
• Anticoagulant Dosing: Days 1 to 4
• Andexxa/placebo Dosing: Day 4
• Safety Follow-Up: Days 5 to 43 (+3)

Reviewer Comment: This study had the same design as 14-503 and is also reasonably well designed to demonstrate that Andexxa can reverse the anticoagulant effects of rivaroxaban in normal healthy volunteers, as evidenced by a reduction in anti-FXa activity.

6.2.3 Population

The eligibility criteria were identical to study 14-503. Please see section 6.1.3 for a discussion of the limitations of the database.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Rivaroxaban was administered by mouth to all subjects at a dose of 20 mg orally once daily (every 24 hours) in the morning from Day 1 through Day 4.

In Part 1 of the study, Andexxa was administered as an IV bolus of 800 mg at a target rate of approximately 30 mg/min (for approximately 27 minutes).

In Part 2 of the study, Andexxa was administered as an IV bolus of 800 mg at a target rate of approximately 30 mg/min (over approximately 27 minutes), followed immediately by a continuous infusion of 960 mg at 8 mg/min (for 120 minutes).

The blinded placebo was administered in the same manner as Andexxa.

Reviewer Comment: As with study 14-503, the applicant states that the dose was chosen based on nonclinical animal model data and data from the Phase 2 study (12-502). This clinical trial did not evaluate the efficacy and safety of the low dose of Andexxa, which Portola is proposing to include as a labeled dose for rivaroxaban. The Phase 2 study (12-502) suggests a dose dependent relationship with nadir levels of unbound Rivaroxaban at Andexxa doses that range from 420 mg bolus only and 800 mg bolus + 8mg/min infusions (Module 2, page 71). The dose dependent relationship between nadir levels of unbound rivaroxaban, and lack of availability of routine monitoring of anti-Xa levels for rivaroxaban to support dose adjustments of Andexxa based on anti-Xa levels in clinical practice makes the utility of the lower dose questionable.

6.2.6 Sites and Centers

The study was conducted at a single site:
West Coast Clinical Trials, Inc.
5630 Cerritos Avenue
Cypress, California 90630

6.2.7 Surveillance/Monitoring

The monitoring schedule mirrored that of study 14-503 (see Section 6.1.7).

6.2.8 Endpoints and Criteria for Study Success

Primary and secondary endpoints for both parts mirrored those of study 14-503 (see Section 6.1.8).

The baseline for the primary endpoint in both parts was the anti-FXa activity just prior to administration of Andexxa/placebo, 4 hours following the Day 4 dose of rivaroxaban.

6.2.9 Statistical Considerations & Statistical Analysis Plan

The statistical analysis plan was the same as study 14-503 (see Section 6.1.9).

6.2.10 Study Population and Disposition

A total of 80 subjects were enrolled and received rivaroxaban (41 in Part 1 and 39 in Part 2). All 80 subjects were randomized (41 subjects in Part 1 [27 Andexxa, 14 placebo] and 39 in Part 2 [26 Andexxa, 13 placebo]).

In part 1, all 41 randomized subjects completed the study.

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.

Reviewer Comment: The number of subjects who were discontinued and the reasons for their discontinuation do not undermine the data or the conclusions drawn about the clinical trial.

6.2.10.1 Populations Enrolled/Analyzed

Safety Analysis Population- all subjects randomized and treated with study medication (Andexxa or placebo).

mITT - all randomized subjects who received any amount of study drug treatment and have baseline value for anti-FXa and at least one of the following time points: +2 minute or +5 minute time point after the end of the bolus (part 1) or all randomized subjects who received any amount of study drug treatment and have baseline for anti-FXa and at least one of the following time points: 110-minute time point during the continuous infusion, -2 minute time point during the continuous infusion, or +5 minute time point after the end of the continuous infusion (part 2).

The subjects in the Safety Analysis and Efficacy Analysis (mITT) Populations were identical: n=41 for part 1 and 39 for part 2.

6.2.10.1.1 Demographics

Of the 80 subjects included in the safety database, most were male (48/80; 60%), white (60/80; 75%), and not Hispanic or Latino (53/80; 66%). The mean (SD) age in Part 1 was 55.2 (3.8) years (median of 55 years with a range of 50 to 65); for Part 2 the mean age was 57.3 (5.16) years (median of 57 years with a range of 50 to 68).

Table 10: Demographic and Baseline Characteristics (Safety Analysis Population)

Demographic or Baseline Parameter	Part 1			Part 2		
	Andexanet (N=27)	Placebo (N=14)	Total (N=41)	Andexanet (N=26)	Placebo (N=13)	Total (N=39)
Age, years						
Mean ±SD	55.6±3.79	54.4±3.84	55.2±3.79	57.0±5.08	58.1±5.45	57.3±5.16
Median (range)	56.0 (50, 65)	53.5 (50, 64)	55.0 (50, 65)	56.0 (50, 68)	57.0 (52, 67)	57.0 (50, 68)
Gender, n (%)						
Male	18 (66.7)	8 (57.1)	26 (63.4)	15 (57.7)	7 (53.8)	22 (56.4)
Female	9 (33.3)	6 (42.9)	15 (36.6)	11 (42.3)	6 (46.2)	17 (43.6)
Ethnicity, n (%)						
Hispanic or Latino	9 (33.3)	4 (28.6)	13 (31.7)	10 (38.5)	4 (30.8)	14 (35.9)
Not Hispanic or Latino	18 (66.7)	10 (71.4)	28 (68.3)	16 (61.5)	9 (69.2)	25 (64.1)
Race, n (%)						
White	22 (81.5)	10 (71.4)	32 (78.0)	20 (76.9)	8 (61.5)	28 (71.8)
Black or African-American	4 (14.8)	2 (14.3)	6 (14.6)	5 (19.2)	5 (38.5)	10 (25.6)
Asian	0	1 (7.1)	1 (2.4)	1 (3.8)	0	1 (2.6)
Other	1 (3.7)	1 (7.1)	2 (4.9)	0	0	0
Body Mass Index, kg/m^2						
Mean ±SD	26.961± 3.3680	25.935± 3.4102	26.610± 3.3757	27.820± 2.9524	27.622± 2.6152	27.754± 2.8113
Median (range)	26.570 (20.64, 32.04)	24.985 (21.14, 31.79)	26.430 (20.64, 32.04)	28.040 (21.61, 32.04)	27.720 (23.47, 31.48)	28.020 (21.61, 32.04)

SD = standard deviation.

Source: CSR 14-504, page 64/138.

Reviewer Comment: As with study 14-503, the study population is adequate to demonstrate the ability of Andexxa to reverse anticoagulation, and is representative of the older population that is likely to use this product. However, as previously noted, the exclusion of patients with renal insufficiency and those with increased risk of thrombosis precludes this population from adequately representing the broader population targeted by the proposed indication.

6.2.10.1.3 Subject Disposition

See Section 6.2.10.

6.2.11 Efficacy Analyses

The study met statistical significant for all primary and secondary efficacy endpoints: significant differences in anti-FXa activity reduction, free rivaroxaban concentration and

restoration of thrombin generation were observed between subjects in the Andexxa and placebo groups.The secondary efficacy analyses were unadjusted for multiplicity.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy analysis compared the primary endpoint of percent change from baseline in anti-FXa activity at the nadir between the two treatment groups using an exact Wilcoxon rank sum test. All hypothesis tests were 2-sided and performed at the 0.05 significance level.

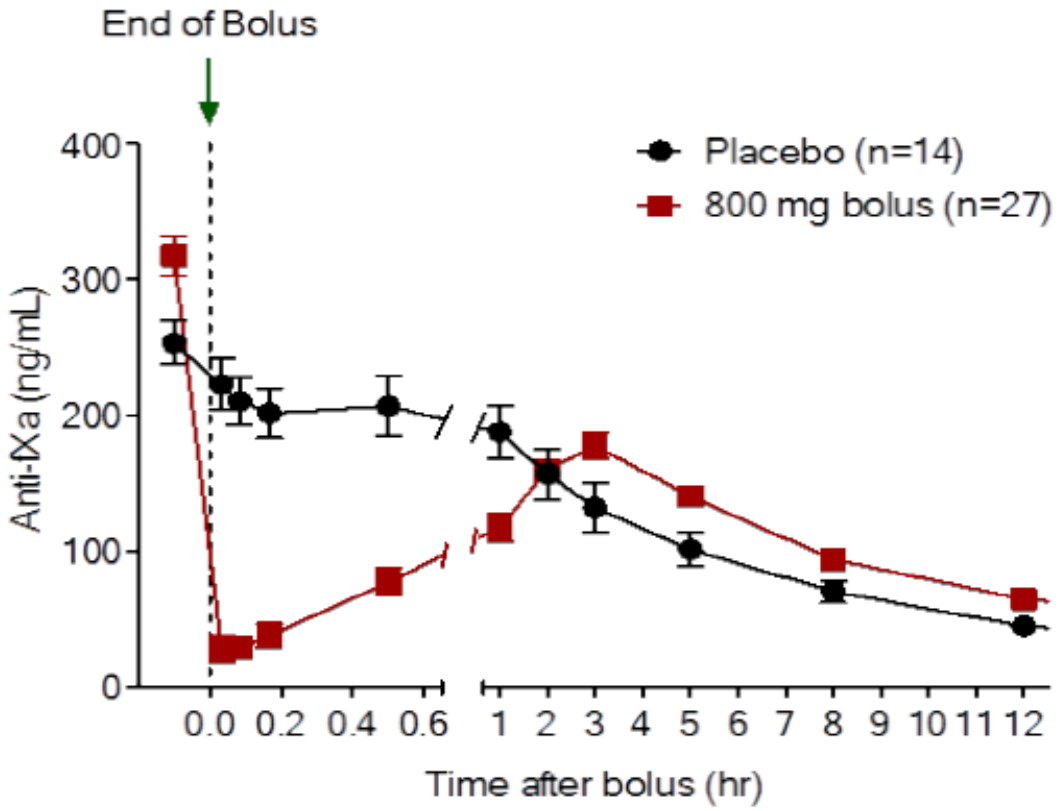
Part 1

In Part 1, the mean (SD) anti-FXa activity levels after anticoagulation with rivaroxaban (baseline) were 318.2 ng/mL (75) and 253.6 ng/mL (60.7) for the Andexxa and control groups, respectively. Nadir levels (SD) of anti-FXa were lowest two minutes after the bolus infusion at 28.2 ng/mL (52.2). Anti-FXa returned to levels observed in the placebo group within 120 minutes after the end of the bolus.

The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -91.1% (10.7%) for the Andexxa group and -18.4% (14.7%; n=13) for the placebo group ($p<0.0001$).

Mean unbound levels of rivaroxaban decreased significantly from baseline levels of 27.3 ng/mL (6.5) to a nadir of 4 ng/mL (3.9) and returned to levels observed in the placebo group within 120 minutes after the end of the bolus.

Figure 5: Anti-FXa Activity following Andexxa Bolus or Placebo (Part 1)



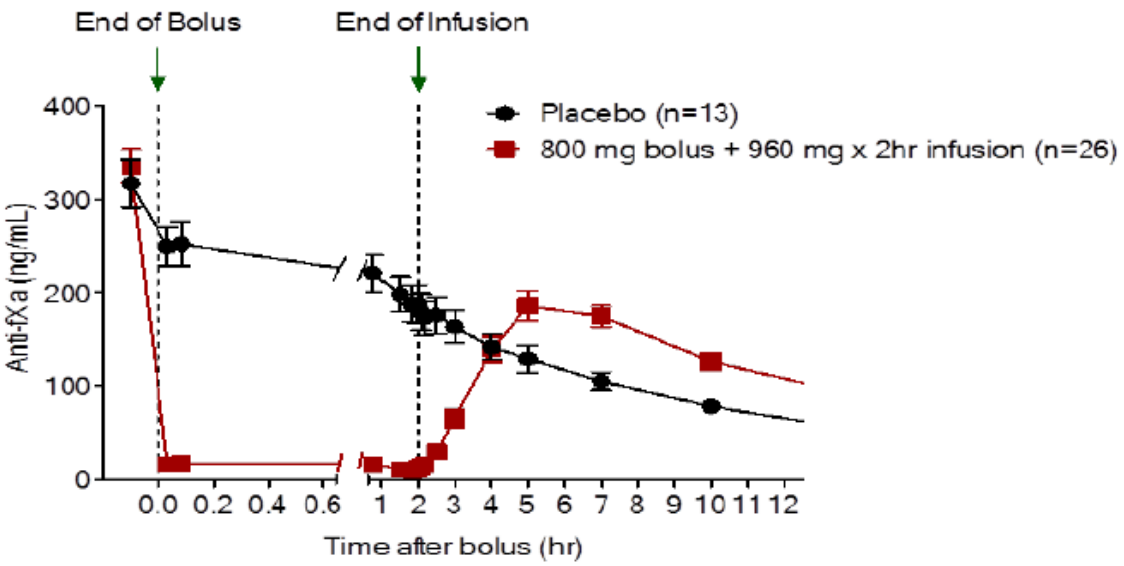
Source: CSR 14-504, page 69/138.

Part 2

In Part 2, the mean (SD) anti-FXa activity levels after anticoagulation with rivaroxaban were 335.3 ng/mL (91) and 317.2 ng/mL (91) for the Andexxa and control groups, respectively.

The mean percent change (SD) from baseline in anti-FXa activity at the nadir was -96.7% (1.8%) for the Andexxa group and -44.7% (11.7%) for the placebo group ($p<0.0001$). All subjects in the Andexxa group had ≥80% reduction in anti-FXa activity. Nadir levels of anti-FXa were lowest 110 minutes after the bolus infusion at a mean of 10.9 ng/mL (6), as compared to levels of 16.8 ng/mL (10.3) at two minutes. Anti-FXa returned to levels observed in the placebo group within 120 minutes after the end of the bolus or bolus plus infusion (Figure 6).

Figure 6: Anti-FXa Activty following Andexxa Bolus + Infusion or Placebo (Part 2)



Source: CSR 14-504, page 70/138.

Reviewer Comment: The observed steady state drug concentrations in this study are comparable to concentrations observed in the phase 3 studies used to support licensure of rivaroxaban. Therefore these results would be generalizable to the target population for which bleeding is observed within the same therapeutic range. Similar to study 14-503, an important limitation of this database is that this study does not inform on the safety and efficacy of reversal in that setting of bleeding due to overanticoagulation (i.e., supratherapeutic levels). In general the pattern of depth and duration of effect is similar to what was observed in 14-503: Andexxa caused a transient significant decline in anti-FXa activity during and shortly following a 2 hour infusion, which was followed by a return of anti-FXa levels in the therapeutic range. In the case of rivaroxaban, rebound anti-FXa levels were higher than observed in the placebo group.

6.2.11.2 Analyses of Secondary Endpoints

Note: Baseline for assessments of anti-FXa activity and free Rivaroxaban concentration is defined as the measurement obtained at 4-hour time point after the apixaban dose on Study Day 4. Baseline for the evlaution of ETP is defined as Day 1 prior to any anticoagulant administration.

Occurrence of ≥80% Reduction in Anti-fXa Activity from its Baseline to Nadir:
All but one subject treated with Andexxa had ≥80% reduction in anti-FXa activity, as compared to no subjects in the placebo group. Per the applicant, subject (b) (6) was enrolled in Part 1, 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.

Change From Baseline in Free Rivaroxaban Concentration at Nadir

In Part 1, mean unbound levels of rivaroxaban decreased significantly from baseline levels of 27.3 ng/mL (6.5) to a nadir of 4 ng/mL (3.9) and returned to levels observed in the placebo group within 120 minutes after the end of the bolus.

In Part 2, mean unbound levels of rivaroxaban decreased significantly from baseline levels of 32.6 ng/mL (7.9) to a nadir of 4 ng/mL (2.8) and returned to levels observed in the placebo group within 240 minutes after the end of the bolus.

Change in ETP from Baseline to its Peak

In Part 1, mean ETP increased from a baseline 369.3±118.3 nmol/min to a peak of 1651.3±417.6 nmol/min). Thrombin generation became similar to placebo at approximately 22 hours post-bolus.

In Part 2, mean ETP increased from a baseline of 379.6±160 nmol/min to a peak of 1862.3±323.9 nmol/min. Thrombin generation (ETP) was maintained during infusion. Thrombin generation became similar to placebo at 14 hours post-bolus. Thrombin generation remained within the baseline range during the study 40-day follow-up period (12 to 960 hours post-dose).

In the placebo arm, thrombin generation did not return to within the baseline range until 24 hours after the bolus in Part 1 and >24 hours after the bolus in Part 2, which the applicant states is "in line with the timeframe for the clearance of unbound rivaroxaban to ineffective levels."

Reviewer Comment: As discussed above, interpretation of these thrombin generation data is limited by lack of data to support that normalization of thrombin generation is necessary to form stable clots and uncertainty about the interpretation of data in the placebo arm as discussed in section 6.1.11.2.

6.2.11.3 Subpopulation Analyses

Due to the size of this individual trial, no inferential subgroup analyses were performed.

6.2.11.4 Dropouts and/or Discontinuations

See Section 6.2.10.1.3.

6.2.11.5 Exploratory and Post Hoc Analyses

The following PD markers were analyzed: (b) (4) .

In Part 1 and Part 2, rivaroxaban increased (b) (4) during the 4 day treatment, which was followed by a more rapid decrease in the mean (b) (4) following Andexxa dosing vs. placebo dosing from Day 4, 2 minutes post-bolus until Day 5.

In Part 1 and Part 2, (b) (4) decrease to a greater extent in the Andexxa group compared with the placebo group, starting immediately (ie, 2 minutes) following the bolus. In Part 1 and Part 2, rivaroxaban increased both PT and aPTT.

Reviewer Comment: As noted previously, (b) (4) tests represent surrogate outcomes that may not reflect clinical efficacy in the context of bleeding.

6.2.12 Safety Analyses

6.2.12.1 Methods

Adverse events (AEs) were coded by using MedDRA and analyzed based on the principle of treatment emergence on or after first infusion with the trial drug. The Safety Analysis Population consisted of all subjects randomized and treated with study drug (Andexxa or placebo). Causality (unrelated, unlikely, possible, and probable) was assessed by the investigator.

6.2.12.2 Overview of Adverse Events

Exposure to Andexxa

In Part 1, all but 3 subjects received the complete single IV bolus of Andexxa 800 mg or placebo; all 3 were dosed simultaneously and experienced leakage from a port in the tubing that began when the infusions were started. The amount of drug that leaked could not be estimated because it had soaked into absorbent mats (in the bedding). No Andexxa was detectable in stored 2-minute and 10-minute specimens.

All subjects in Part 2 received the full dose of Andexxa.

Treatment Emergent Adverse Events

AEs occurred in 33/80 (41%) subjects, including 23/53 (43%) treated with Andexxa and 10/27 (37%) treated in the placebo group. All were mild in severity except for a moderate AE of presyncope in subject (b) (6) on Day 1 from 16:14 to 18:00 after receipt of Andexxa from 13:21 to 13:48.

In Part 1, the incidences of TEAEs in the Andexxa and placebo groups were 44.4% and 28.6%, respectively. The most common AE occurring with >10% difference in incidence between the Andexxa and placebo was Infusion-Related Reaction.

In Part 2, the incidences of TEAEs in the Andexxa and placebo groups were 42.3% and 46.2%, respectively. The most common AEs were Muscle Spasms and Constipation in the Andexxa group. There were no AEs occurring with >10% differences in incidence between the Andexxa and placebo groups.

Table 11: Overview of Adverse Events (Safety Analysis Population)

Category Subjects With ≥1 AE	Part 1 (n=41)		Part 2 (n=39)	
	Andexxa (n=27) n (%)	Placebo (n=14) n (%)	Andexxa (n=26) n (%)	Placebo (n=13) n (%)
All TEAEs	12 (44.4)	4 (28.6)	11 (42.3)	6 (46.2)
AEs within the first hour of study drug exposure	7 (25.9)	0	0	1 (7.7)
TEAEs related to study drug	5 (18.5)	1 (7.7)	1 (3.8)	2 (15.4)
SAE	0	0	0	0

AEs of special interest[a]	0	0	0	0
Premature discontinuation of study drug due to AE	0	0	0	0
Withdrawals from study due to AE	0	0	0	0
Deaths	0	0	0	0

AE = adverse events; SAE = serious AEs; TEAE = treatment-emergent AE.
[a] = AE of special interest were VTE of any severity, moderate or severe infusion reaction, AST, or ALT >3×ULN if associated with a total bilirubin >2×ULN, or AST or ALT >3×ULN or total bilirubin >2×ULN if associated with clinical signs or symptoms of liver injury (eg, jaundice).
Source: Adapted from CSR 14-504, page 93/138.

6.2.12.3 Deaths
There were no deaths.

6.2.12.4 Nonfatal Serious Adverse Events

There were no SAEs.

6.2.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events:
No confirmed thromboembolic events were reported; however, elevations in at least one of the thrombogenic markers measured (d-dimer, prothrombin fragments 1+2) was noted in subjects dosed with Andexxa in both parts of the study.

Immunogenicity
In Part 1, 4/27 (14.8%) subjects in the Andexxa group had anti-andexanet antibodies detected:

- Subject (b) (6) had anti-andexanet antibodies detected at Day 36 (1:80 titer) and Day 43 (1:160 titer)
- Subject (b) (6) had anti-andexanet antibodies detected at Day 15 (1:640 titer), Day 36 (1:20 titer), and Day 43 (1:40 titer)
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 15 (1:160 titer), at OPV Day 36 (1:20 titer), and at OPV Day 43 (1:20 titer)
- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 36 (1:40 titer) and at OPV Day 43 (1:80 titer)

In Part 1, 1/14 (7.1%) subject in the placebo group had anti-andexanet antibodies detected:

- Subject (b) (6) had anti-andexanet antibodies detected at INPT Day 1 (1:20 titer), at OPV Day 15 and OPV Day 36 (1:10 titer each time point), and at OPV Day 43 (1:20 titer)

In Part 2, 2/26 (7.7%) subjects in the andexanet group had anti-andexanet antibodies detected:

- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 15 (1:20 titer), OPV Day 36 (1:20 titer), and OPV Day 43 (1:40 titer)

- Subject (b) (6) had anti-andexanet antibodies detected at OPV Day 15 (<1:10 titer) and OPV Day 43 (<1:10 titer)

Hypersensitivity/Allergic Reactions
All Infusion-Related Reaction AEs were mild in severity, considered by the Investigator as related to study drug, and resolved.

In Part 1, 5 subjects (18.5%) in the Andexxa group and no subjects in the placebo group had Infusion-Related Reactions. In Part 2, no subjects had Infusion-Related Reactions.

Subjects in the Andexxa Group:

- Subject (b) (6) had 2 AEs of mild infusion-related reaction (urticaria and pruritus) that were considered related to Andexxa. No action was taken and the AEs resolved.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (flushing) that was considered related to Andexxa. No action was taken and the AEs resolved.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (flushing) that was considered related to Andexxa. No action was taken and the AEs resolved.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (erythematous rash) that was considered related to Andexxa. No action was taken and the AEs resolved.
- Subject (b) (6) had 1 AE of mild infusion-related reaction (neck pain) that was considered related to Andexxa. No action was taken and the AEs resolved.

Reviewer Comment: As discussed above, the risk of immunogenicity is a major concern for this product. The imbalance in infusion-related reactions at this higher dose is noted, and will be adequately described in labeling, if approved. The incidence of 18.5% is not a safety concern as all were mild reactions and did not warrant additional intervention. The assessments of causality in each case were appropriate.

6.2.12.6 Clinical Test Results

Coagulation Tests
Part 1
Five (18.5%) subjects in the Andexxa group had a D-Dimer value that was >2×ULN at any time point. The latest time point of a D-Dimer elevation >2×ULN was at OPV Day 43, and this occurred in 2 subjects (Subjects (b) (6) and (b) (6)) in the Andexxa group and no subjects in the placebo group:

- Subject (b) (6) had normal values before Day 36
- Subject (b) (6) had elevations >2×ULN from 2 min postbolus through Day 5, elevations <ULN on Day 6 through Discharge Day 8, and elevations >2×ULN on Day 15 through Day 43.

Twelve (44.4%) subjects in the Andexxa group and 2 (14.3%) subjects in the placebo group had a prothrombin fragment 1+2 value that was >2×ULN at any time point. The latest time point of a prothrombin fragment 1+2 elevation >2×ULN was Day 43, and this

occurred in 2 subjects (Subjects (b) (6) and (b) (6)) in the Andexxa group and no subjects in the placebo group.

- Subject (b) (6) had no elevations before Day 43.
- Subject (b) (6) had elevations >2×ULN at Day 6 and Day 15.

Part 2
Eleven (40.7%) subjects in the Andexxa group had a D-Dimer value that was >2×ULN at any time point. Subject (b) (6) had a D-Dimer elevation that was>2×ULN at Day 43.

Twenty (76.9%) subjects in the Andexxa group and 1 (0.77%) subject in the placebo group had a prothrombin fragment 1+2 value that was >2×ULN at any time point following Andexxa administration. The latest time point of a prothrombin fragment 1+2 elevation >2× the ULN was OPV Day 43, and this occurred in 1 subject (Subject (b) (6)) in the Andexxa group. Subject (b) (6) also had elevations >2×ULN at 5 minutes and 300 minutes post infusion but no other elevations that were >2×ULN.

12-lead Electrocardiograms
In Part 1, a newly abnormal PR interval > 200 msec was reported for 1 subject in the Andexxa group and 1 subject in the placebo group:

- Subject (b) (6) in the Andexxa group had a baseline pre-dose PR interval of 192 msec and a PR interval on Day 43 of 208 msec (other PR values were < 200 msec).

In Part 2, PR intervals > 200 msec were reported for two subjects in the Andexxa group and no subjects in the placebo group:

- Subject (b) (6) had a baseline PR interval 190 msec; Inpatient Day 4 at 5 minute post-bolus PR was 202 msec.
- Subject (b) (6) had baseline pre-dose PR interval 197 msec; Inpatient Day 4 at 5 minute post-bolus PR was 219 msec; Inpatient Day 4 at 5 minute post-infusion PR was 212 msec; Discharge Day 8 PR was 217 msec and OPV Day PR was 205 and 201 msec. (Note: subjects had pre-dose PR intervals > 190 msec).

Reviewer Comment: As per my comments in Section 6.1.12.6, these findings do not suggest that Andexxa causes PR prolongation. A review of the reported AEs did not identify other causes of PR prolongation, such as calcium channel-blockade and increase in vagal tone as evidenced by increased reports of bradycardia, constipation, or worsened reflux.

Creatinine
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.

Reviewer Comment: These findings are not indicative of acute kidney injury.

6.2.12.7 Dropouts and/or Discontinuations

No subjects in this study prematurely discontinued study drug administration due to an AE.

6.2.13 Study Summary and Conclusions

These findings are consistent with findings from 14-503 in that they demonstrate that Andexxa can rapidly reverse anticoagulation for the duration of the infusion and reaffirms the conclusion that a longer infusion or repeat dosing may be required, particularly for indications where sustained reversal is warranted (e.g., ICH). No new safety signals were identified in this study.

6.1 Trial #3

14-505: Prospective, Open-Label Study of Andexanet Alfa In Patients Receiving A Factor Xa Inhibitor Who Have Acute Major Bleeding (Annexa-4)

This trial is ongoing and, following protocol amendment, will serve as the confirmatory study that is required under the Accelerated Approval Program.

6.3.1 Objectives (Primary, Secondary, etc)

Primary Objectives:
The two primary hierarchical endpoints are:

1. The percent change from baseline in anti-FXa activity to the nadir from the evaluation period (where the evaluation period starts 5 minutes following the end of the Andexxa bolus and ends just prior to the end of the Andexxa infusion)
2. The achievement of hemostatic efficacy of stopping an ongoing major bleed at 12 hours from the end of the Andexxa infusion.

Secondary Efficacy Objective:

- To assess the relationship between decrease in anti-FXa activity and the achievement of hemostatic efficacy in patients receiving FXa inhibitors who have acute major bleeding and reduced FXa activity.

Exploratory Objectives:

- For patients receiving apixaban or rivaroxaban, to evaluate the decrease in the free fraction of the FXa inhibitor following Andexxa treatment.
- To evaluate the use of red blood cells transfusions.
- To evaluate the use of other blood products and hemostatic agents.

Safety Objectives:

- To evaluate the overall safety of Andexxa, including adjudicated TEs and antibodies to FX, FXa, and Andexxa.
- To evaluate the 30-day all-cause mortality.

6.3.2 Design Overview

The trial is designed as a multicenter, prospective, open-label, single armed study of Andexxa in approximately 250 subjects (162 evaluable) presenting with acute major bleeding who have recently received one of the following direct or indirect FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Evaluable subjects are required to have pre-treatment (baseline) > 75ng/nl of anti-Xa level following central laboratory evaluations performed following treatment with Andexxa.

Patients are primarily enrolled in the emergency department (ED) upon presentation with an acute major bleeding episode; however, patients who experience an acute major bleeding episode while hospitalized in various inpatient units may also be enrolled.

Following the start of Andexxa treatment, subjects will be 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 hemorrhage (ICH); and transfusion-corrected hemoglobin and hematocrit for non-visible bleeding. AEs are followed through Study Day 3, and related AEs and survival will be followed through the Day 30 post-treatment visit.

Hemostatic efficacy will be adjudicated by an independent Endpoint Adjudication Committee (EAC) using a three-point rating scale of excellent (effective), good (effective), or poor/none (not effective). The EAC will also adjudicate all potential thrombotic events and will be blinded to all anti-FXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter.

The study duration for any individual patient will be up to 37 days:
• Screening Period: <1 day (Day 1)
• Treatment Period: <1 day (Day 1)
• Safety Evaluation Period: 3 days (Days 1–3)
• Extended Safety Follow-Up Period (related AEs, survival): ~26 days (Day 4 to the Day 30 study visit)

Review Comment: During early discussions about trial design for the confirmatory study, FDA advised that a RCT would be necessary to evaluate the safety and efficacy of this product. Portola expressed concerns about conducting a RCT because of the time it would take to conduct such a study, the feasibility in trial design as it relates to the identification of a control population, and the selection of hemostatic endpoints. FDA acknowledged that a RCT would likely take several years to complete, but also maintained that safety concerns related to the potential thrombogenicity of the product need further evaluation in an adequately controlled trial. In considering the feasibility issues of a RCT, the clinical review team worked closely with Portola to identify an adequate trial design that would be least burdensome but that would also yield data that was interpretable. These designs included randomizing treatment facilities (cluster randomization), conducting a

dose-controlled study in the target population, obtaining prospectively collected data from bleeding subjects with baseline characteristics that were similar to the cohort being studied (nonrandomized concurrent control), obtaining control data from centers where the clinical trials of Andexxa will be conducted (crossover design), and the use of a historical control data. Portola chose a historical controlled trial (HCT) design and proposed to use the results from a study of vitamin-K antagonist (VKA)-treated patients with acute major bleeding as a benchmark (Sarode, *et al*). The clinical review team did not consider this to be an adequate control population as the mechanism of action and rates of major bleeding in patients receiving VKAs are dissimilar to FXa inhibitors. The features expected in a well-designed HCT included not only having a control group that was treated with the same anticoagulant, but also having a control group with similar eligibility and evaluation criteria and similar prognostic factors. FDA advised that a single arm cohort design may be acceptable, provided an adequate comparative database can be identified or prospectively generated. During further discussion under the Type A dispute resolution process, Portola agreed to conduct a prospective Usual Care Cohort study. This study is expected to enroll bleeding patients with similar bleeding profile (seriousness and types of bleeds) and baseline characteristics through similar inclusion/exclusion criteria as the confirmatory study to ensure a comparable study population. Propensity scoring will be used to compare hemostatic outcomes to those observed in the ongoing confirmatory study.

A final design of the confirmatory study and the Usual Care Cohort study has not been approved by FDA, but will need to be negotiated and agreed upon prior to licensure as per regulations.

6.3.3 Population

Eligibility Criteria:

Key Inclusion Criteria

- The patient must be at least 18 years old at the time of screening;
- The patient must have an acute major bleeding episode requiring urgent reversal of anticoagulation.

Acute major bleeding requiring urgent reversal of anticoagulation is defined by at least ONE of the following:

- Acute overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained;
- Acute overt bleeding associated with a fall in hemoglobin level by ≥2 g/dL, OR a Hb ≤ 8 g/dL if no baseline Hb is available OR, in the opinion of the investigator that the patient's hemoglobin will fall to ≤ 8 g/dL with resuscitation;
- Acute symptomatic bleeding in a critical area or organ, such as, retroperitoneal, intra-articular or pericardial, intracranial or intramuscular

with compartment syndrome. Patients with intracranial bleeding must have undergone a head CT or MRI scan demonstrating the intracranial bleeding.

Key Exclusion Criteria

- The patient is scheduled to undergo surgery in less than 12 hours with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes
- A patient with ICH has any of the following:
  - Glasgow coma score < 7
  - Estimated intracerebral hematoma volume >60 cc as assessed by the CT or MRI
- The patient has an expected survival of less than 1 month
- The patient has a recent history (within 2 weeks) of a diagnosed thrombotic event as follows: myocardial infarction, disseminated intravascular coagulation, cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening
- The patient is pregnant or a lactating female
- The patient has received any of the following drugs or blood products within 7 days or Screening:
  a. Vitamin K antagonist (e.g., warfarin);
  b. Dabigatran;
  c. Prothrombin Complex Concentrate products or rFVIIa;
  d. Whole blood, plasma fractions

Reviewer Comment: The study criteria allow for enrollment of a heterogeneous patient population, from the standpoint of sites of bleeding, comorbidities and bleeding profiles, which limit the interpretability of the observed outcomes in this single arm study. Furthermore, the subjective nature of inclusion criteria for non-visible bleeding (*e.g.*, relying on the opinion of the investigator to predict that the patient's hemoglobin will fall to ≤ 8 g/dL, including non-specific parameters, such as mental confusion and poor skin perfusion, for hemodynamic compromise) allows subjects who lack clinical evidence of acute overt bleeding to be included in the study. Because the data from non-visible bleeding (GI bleeding in particular) were considered uninterpretable (see section 7.1.7) and because the unmet medical need may be greatest in ICH, FDA advised Portola to revise their study population to include subjects experiencing ICH bleeds only. FDA advised that a revised study of ICH would result in a relatively homogenous study population, which would make it more feasible to objectively measure bleeding pre and post Andexxa treatment and

improve the interpretability of the data. In addition, such an ICH study would allow for the evaluation of efficacy in a population with the highest morbidity and mortality risk from FXa inhibitor-related bleeding, and would address the uncertainities regarding efficacy where extended duration of reversal is anticipated. Improved homogeneity in the eligible population is also expected to improve the ability to match the population to the Usual Care Cohort study. FDA's position is that while confirmation of hemostasis could be conducted in any of the bleeding populations (*e.g.*, ICH, GI bleed, etc), the uninterpretability of the results in GI bleeding could only be rectified to a certain extent through protocol revisions (*e.g.*, revising eligibility requirements to have confirmed bleeding by endoscopy, excluding subjects presenting with melena without visible bleeding, requiring subjects to undergo follow up endoscopies rather than reliance on correction of Hb). Even if changes to the protocol along these lines were implemented, the duration of reversal, a key issue to approval for an ICH indication, would likely not be adequately addressed from a GI bleeding study. FDA's position is that establishing efficacy in the ICH population would be adequate to extend the indication to other acute major bleeding types. Recommended revisions to the confirmatory study include enriching the population to subjects with ICH who are at the highest risk for re-bleed, including those eligible for treatment within the first 3 hours of their bleed (SGE neurology consultant noted that "when evaluating a treatment intended to stop further bleeding in these patients, it would be much more likely to see a beneficial effect if it is given very early after bleeding onset, and failure to include such patients in trials of pro-coagulant drugs has been one explanation for their failure to translate to clinical benefit in trials to date"); those with imaging features that are considered important in predicting further bleeding after spontaneous ICH and may also be important after FXa inhibitor therapy, such as the "spot" sign seen on CT scans, irregularity of the hematoma border, and variability in hematoma density; and those with supratentorial bleeds. Additionally, stratification of enrollment based on time from last dose should be considered.

6.3.4 Study Treatments or Agents Mandated by the Protocol

There are two dosing regimens. Recommended dosage is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor:

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

FXa Inhibitor	FXa Inhibitor Last Dose	Proposed Dose of Andexxa Based on Administered Dose and Timing of Last Dose of FXa Inhibitor Prior to Initiation of Reversal*	
		<7 Hours or Unknown	≥ 7 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg / Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg / Unknown	High Dose	
(b) (4)			

Reviewer Comment: The start of the Andexxa bolus must be within 18 hours following the last dose of FXa inhibitor, if the timing of the last dose is known, which FDA considers too remote from treatment. Both CDER and SGE neurology consultants agree that this time interval should be decreased. SGE consultant notes that "While having received a fXa inhibitor within the past 18 hours (current inclusion criteria) would put the patient at increased risk of further bleeding, that risk would be higher in a patient seen 3 hours after dosing than at 17 hours when presumably anti-fXa activity would be less."

6.3.8 Endpoints and Criteria for Study Success

The following co-primary endpoints are being evaluated:

- The percentage change from baseline in anti-Xa activity to the nadir in the evaluation period
- Achievement of hemostatic efficacy of stopping an ongoing major bleed at 12 hours from the end of Andexxa infusion as rated by independent EAC assessments.

Criteria for Study Success

The study will be considered to have met the first primary efficacy objective if there is a statistically significant ($p<0.05$) percent decrease in anti-FXa activity from the pre-treatment baseline to the evaluation period nadir (where the evaluation period starts 5 minutes following the end of the Andexxa bolus and ends just prior to the end of the Andexxa infusion).

The study will be considered to have met the second primary efficacy objective if the proportion of patients with excellent or good hemostasis (as adjudicated by the independent EAC) is statistically significantly higher than 50% ($p<0.05$). The second co-primary efficacy endpoint is only tested if the first co-primary endpoint yields a statistically significant positive result (hierarchical analysis). Both co-primary endpoints must achieve statistical significance in order for the study to be considered a success.

Reviewer Comment: FDA previously advised Portola that a clinical endpoint should be the primary endpoint for the confirmatory study, and that the surrogate endpoint be changed to a secondary endpoint. As a secondary endpoint, correlation between this endpoint and hemostatic efficacy could still be examined. FDA advised that if the confirmatory trial were to demonstrate clinically meaningful and statistically significant hemostatic efficacy in the absence of positive findings for the biochemical surrogate, such an outcome would still be supportive of a conversion from accelerated to regular approval after submission and review of the phase 4 PMR final study report. FDA advised this because clinical trials of warfarin were unable to demonstrate correlation of reversal of anticoagulation (corrected international normalized ratio) with improved clinical outcomes (Dowlatshahi, *et al*). FDA also advised that it may be difficult to attribute efficacy at the 12 hour time-point to Andexxa given the short duration of reduction in anti-FXa activity and the elimination kinetics of Andexxa. Furthermore, given that the study includes subjects who received FXa inhibitors within 18 hours prior to Andexxa administration; the interval between the prior dose of FXa inhibitor and efficacy assessment may extend to approximately 32 hours. Successful control of bleeding may result from reduced levels of FXa inhibitors during the 32 hour interval that would be independent of any effects from Andexxa administration. Furthermore, cutoff values for hematoma expansion, as defined in the phase 3b/4 protocol, are not specific for the type of ICH (e.g., subdural hematoma (SDH) versus cerebellar). Therefore, the current design of the study will result in success even if the drug has no effect. FDA has provided advice regarding the revised design of the ongoing confirmatory study with regard to inclusion criteria and assessment of primary outcomes as described above.

6.3.9 Statistical Considerations & Statistical Analysis Plan

Hemostatic efficacy will be determined by the EAC as excellent, good, or poor/none based on the pre-specified definitions (Appendix III). These three categories will be collapsed into two categories for analysis (excellent/good vs. poor/none).

Reviewer Comment: As no additional type 1 error rate adjustments are proposed, both endpoints need to be successful in order to call the study successful.

6.3.10 Study Population and Disposition

As of March 11, 2016, 77 (out of 250 planned) subjects have been enrolled and treated with Andexxa, of which 35 had information available for the evaluation of efficacy. Of the 35 subjects with available information, 18 (51%) were males and 17 (49%) were

females with a mean age of 77.6 years (median: 81 years with a range of 55 to 95). A total of 13 subjects were previously treated with rivaroxaban, 18 with apixaban, and 4 with enoxaparin. The majority of bleeding events were ICH (n=13) and gastrointestinal (GI; n=16). The remaining were retroperitoneal (n=3), visible (n=1), pericardial (n=1), and intra-articular (n=1).

Of the 18 subjects presenting with acute major bleeding who recently received apixaban, 7 presented with GI bleeds, 9 with ICH, 1 with visible, and 1 with a retroperitoneal bleed. Of the 13 subjects who recently received rivaroxaban, 8 presented with GI bleeds, 4 with ICH and 1 with a retroperitoneal bleed. The remaining 4 subjects had enoxaparin-related bleeding events, including 2 GI bleeds, 1 pericardial and 1 retroperitoneal.

A total of 22/35 (63%) of evaluable subjects had moderate impaired renal function (eGFR <60 mL/min/1.73 m^2). Of these, 4 subjects had baseline anti-FXa levels that were greater than 2 standard deviations from the mean anti-FXa activity levels observed in healthy volunteer studies. *Note: renal clearance and the amount of Andexxa excreted unchanged in urine could not be established in clinical trials because urinary Andexxa concentrations were below the limit of quantification. In addition, serum chemistries were obtained at baseline only so assessment of sucrose-related toxicity was not possible.*

6.3.10.1 Populations Enrolled/Analyzed

Per the protocol, the primary analysis will be done on the Efficacy Analysis Population (EAP), which includes subjects whose baseline anti-FXa activity is >75 ng/mL, which Portola states corresponds to approximately the anti-FXa level achieved at twice the mean plasma concentration at 24 hours after administration of the highest approved doses for rivaroxaban and at 12 hours for apixaban.

Reviewer Comment: FDA previously advised that the primary analysis should be done on the intent-to-treat population and not the EAP as the EAP is considered a subgroup and that FDA would consider both populations during the review of the BLA. It is unclear how the 75 ng/mL relates to the degree of anticoagulation that would be expected to aggravate bleeding. In the clinical setting anti-FXa levels will not be available at the time of treatment; any patient with a serious or life-threatening bleed will be given Andexxa therefore it is important to have an assessment of safety and efficacy in all treated subjects, including those with levels below 75 ng/mL. In the current study 8/35 (23%) of subjects had levels below 75 ng/mL, which is a considerable number of patients that will be exposed to Andexxa if you consider the estimated incidence of serious bleeding events. Because a companion diagnostic is not available to provide anti-FXa levels in real time, the benefit-risk profile of Andexxa in this subgroup should be also be favorable.

Of the 35 subjects with available information, 2 subjects ((b) (6) and (b) (6)) had bleeds that were not considered major bleeds and adjudication of efficacy for one subject ((b) (6)) is pending. An additional subject ((b) (6)) had undetectable anti-FXa levels at baseline (<4 ng/mL), suggesting that the bleed was not from anticoagulation. These

subjects were excluded from the analysis done by this reviewer. In addition, two subjects ((b) (6) and (b) (6)) had bleeds that were considered not evaluable by the EAC.

6.3.11 Efficacy Analyses

Hemostatic Efficacy

Overall, per the applicant, 27/35 (77%) of subjects achieved excellent/good hemostatic efficacy; however, this analysis included subjects that did not have a major bleed (n=2), a pending efficacy rating (n=1), or detectable anti-FXa levels of ≥4 ng/mL (n=1). Exclusion of these subjects results in similar efficacy, based on the sponsors adjuciation reports, of 24/31 (77%). FDA was unable to confirm the successful adjucations in many cases due to uncertainty about the acuteness of bleeding events and evaluations for cessation of bleeding for non-visible bleeds (see section 7.1.7). As discussed above, two subjects ((b) (6) and (b) (6)) had bleeds that were not evaluable by the EAC. Narratives for the 5 subjects with efficacy assessments of 'poor/none' by the EAC are provided below:

- Subject (b) (6) was a 90 year-old white male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with a SDH due to blunt trauma. The subject was assigned to low dose Andexxa. Anti-FXa levels were reduced by 83% following the Andexxa infusion (baseline anti-FXa was 176.1 ng/mL). The 1-hour post-infusion CT showed a significant increase in thickness from 12.23 mm at baseline to 21 mm. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Poor/none.' The subject was discharged from the hospital on SD 3 and re-anticoagulated with rivaroxaban, 20 mg once daily.
- Subject (b) (6) was an 84 year-old, white female taking apixaban 2.5 mg bid for atrial fibrillation who presented to the ED with a CT-confirmed intraparenchymal bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 95% following the Andexxa infusion (baseline anti-FXa was 117.7 ng/mL). The subject had an interim development of intraventricular hemorrhage noted after the 1 hr post-infusion assessment that was not documented at baseline.
- Subject (b) (6) was an 86 year-old male taking apixaban 2.5 mg twice daily for atrial fibrillation and portal venous thrombosis who presented to the ED with a GI bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. The EAC commented that there was a significant decreased in the corrected hematocrit and hemoglobin, despite multiple blood transfusions. An EGD and colonoscopy were unrevealing. Anti-FXa levels were reduced by 94% following the Andexxa infusion (baseline anti-FXa was 147.3 ng/mL).
- Subject (b) (6) was a 78 year-old white female taking rivaroxaban 15 mg once daily for atrial fibrillation, who presented to the ED with a retroperitoneal bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 87% following the Andexxa infusion (baseline anti-FXa was 389.1 ng/mL). The adjudication committee noted

that bleed was reported as retroperitoneal, however, assessed as muscular/skeletal (M/S). This bleed should have been assessed as other-non-visible bleeding with the CT scans or images used for assessment. The site had not repeated the CT scan at the 12-hour assessment, so there were no comparisons for the size of the bleed. Per the applicant, the source documents and CRFs showed that the pain stayed the same up to the 12-hour assessment, and hemoglobin had fallen after the infusion. Therefore, the final post-treatment hemostatic efficacy assessment by the adjudication committee is poor/none.

- Subject (b) (6) was a 90 year-old white male taking apixaban 2.5 mg, twice daily for atrial fibrillation, who presented at the ED with an ICH noted specifically to include a subarachnoid hemorrhage, and separately a nonvisible bleed (respiratory tract - pleural). The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 89% following the Andexxa infusion (baseline anti-FXa was 65.2 ng/mL). The intracranial bleeding continued to expand -8.26 mL (9 hours pre-bolus), 12.30 mL (right before bolus), 63.90 mL (4 hours postinfusion), 42.1 mL (12 hours post-infusion).

For apixaban, 18 subjects had available information for evaluation by the EAC. A total of 15 subjects were considered major bleeds, had detectable anti-FXa activity levels at baseline and an efficacy rating by the EAC, including 1 that was treated for a retroperitoneal bleed, 1 for a visible bleed, 1 for intra-articular bleed, 5 for GI bleeds, and 7 with ICH. All subjects received the low dose Andexxa regimen (400 mg bolus + 480 mg infusion). A total of 10/15 (67%) of subjects achieved excellent/good hemostatic efficacy; 3 (19%) bleeds received 'poor/none' ratings by the EAC; and 2 bleeds were not evaluable.

For rivaroxaban, 12 out of 13 subjects with available information were considered to have major bleeds, including 1 that was retroperitoneal, 7 that were GI, and 4 that were ICH bleeds. Two subjects received the high dose Andexxa regimen (800 mg bolus + 960 mg infusion) and the other subjects received the low dose. A total of 10/12 (83%) of subjects achieved excellent/good hemostatic efficacy; 2 (17%) bleeds received 'poor/none' ratings by the EAC.

For enoxaparin, all 4 subjects achieved excellent/good hemostatic efficacy.

Percentage Change From Baseline in Anti-FXa Activity to the Nadir

Note: as a conservation approach, anti-FXa levels reported as <4 ng/mL were assigned a numerical value of 4 ng/mL, rather than zero.

Apixaban

The mean baseline anti-FXa activity level for the 15 subjects with major bleeds and detectable anti-FXa activity levels was 222.3 ng/mL (median 147.3 ng/mL; range: 49.1 to >950 ng/mL). For the 14 subjects with available data, the mean percent change from baseline anti-FXa activity to post-bolus was -79% (median -92%; range -23 to -97%). For the 13 subjects with available data, the mean percent change from baseline anti-FXa

activity to post-infusion was -79% (median -92%; range -42 to -95%). *Note: although 16 subjects were considered to have had a major bleed, subject* (b) (6) *had a baseline level of <4 ng/mL suggesting that the cause of the bleed was not directly related to anticoagulation and therefore was excluded from the analysis by this reviewer.*

The mean anti-FXa activity at four hours post-infusion was 180.2 ng/mL. Mean post-infusion levels at 8 and 12 hours were 165.1 and 129.7 ng/mL, respectively. Anti-FXa activity levels were not obtained after the 12 hour time-point.

Three subjects had baseline levels that were ≥2 SD above the mean from the phase 3, part 2 study: [subjects (b) (6) (retroperitoneal/skin bleed; anti-FXa activity level: 498 ng/mL), (b) (6) (GI; 487.1) and (b) (6) (GI; >950)]. For all three subjects with higher baseline values, the percent reduction after the infusion was <50%. *Note: percent reduction for subject* (b) (6) *and* (b) (6) *was higher after the bolus (68% and 78%) but anti-FXa levels increased during the infusion, resulting in a lower percent reduction after the infusion.*

Exclusion of the data from subjects with levels that were ≥2 SD resulted in a mean percent change in anti-FXa activity of -92.4%.

Reviewer Comment: Hemostatic efficacy was successful for all three bleeds, despite the less than anticipated percent reduction in nadir anti-FXa levels, suggesting that correlation between anti-FXa levels and hemostatic efficacy may be difficult to establish.

Rivaroxaban
The mean baseline anti-FXa activity level for the 12 subjects was 276.9 ng/mL (SD: 61 ng/mL; median 200.4 ng/mL; range: 134.7 to 862.4 ng/mL). The mean percent change from baseline anti-FXa activity to post bolus was -81% (median -92%, range -22 to -98%). The mean percent change from baseline anti-FXa activity to post infusion was -79% (median -86.5%, range -42 to -98%).

For the 10 subjects with available data, the mean anti-FXa activity at four hours post-infusion was 173.1 ng/mL. Mean post-infusion levels at 8 and 12 hours were 141.1 and 109.8 ng/mL, respectively. Anti-FXa activity levels were not obtained after the 12 hour time-point.

One subject had baseline levels that were ≥2 SD above the mean from the phase 3, part 2 study: subject (b) (6) had an anti-FXa activity level of 862 ng/mL at baseline; treatment with Andexxa resulted in 44% of anti-FXa activity. Hemostatic efficacy was excellent.

Two subjects out of the 10 subjects treated with the low dose had lower-than-expected decreases in mean percent changes in anti-FXa activity, despite having levels within the expected therapeutic range:

- Subject (b) (6) was a 67 year-old male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with bright red blood per rectum, which started 2 hours and 25 minutes after the last dose of rivaroxaban. He received the

low dose of Andexxa (time from last dose of anticoagulant to Andexxa was 9 hours and 40 minutes). Mean percent changes post-bolus and post-infusion were:

Anti-FXa activity (baseline)	Anti-FXa after bolus	Percent reduction	Anti-FXa after infusion	Percent reduction
227.8	178.5	22	132.8	42

- Subject (b) (6) was a 77 year-old African-American female taking rivaroxaban 20 mg once daily for venous thromboembolism prevention who presented to the ED with a GI bleed 11 hours after the last dose of rivaroxaban. She received the low dose of Andexxa (time from last dose of anticoagulant to Andexxa was 18 hours and 20 minutes). Mean percent changes post-bolus and post-infusion were:

Anti-FXa activity (baseline)	Anti-FXa after bolus	Percent reduction	Anti-FXa after infusion	Percent reduction
295.2	6.3	98	136.5	54

Mean unbound levels of rivaroxaban decreased from baseline levels of 21.1 ng/mL to 6.6 ng/mL post-infusion (median 18.1, range: 10.4 to 48.5). Mean levels at 4, 8, and 12 hours were 15, 9.7 and 5.2, respectively.

Enoxaparin
Four subjects with acute major bleeding while on enoxaparin were treated with Andexxa, including 2 subjects with GI bleeding and 1 subject with pericardial bleeding. Three subjects received high dose Andexxa. The mean baseline anti-FXa activity level for these 12 subjects was 0.42 ng/mL (median 0.46 ng/mL; range: 0.13 to 0.61 ng/mL). For the 3 subjects with available data, the mean percent change from baseline anti-FXa activity to post infusion was -51%.

Reviewer Comment: The clinical significance of these findings is limited by the small sample size and the lack of a control group. FDA previously advised Portola that safety and efficacy data in the target population was required at the time of BLA filing, and that Portola should consider the number of subjects that will be able to demonstrate correlation with a formal statistical analysis. During Type A meetings Portola claimed that this requirement would delay their clinical development and BLA filing, and therefore OBRR management agreed to make this a review issue. As stated previously, FDA did not accept anti-FXa activity as a surrogate reasonably likely to predict outcomes because of the dual mechanism of action of this drug, which precludes review of these data for this indication under accelerated approval. Furthermore, in the absence of adequate phase 2 and 3 enoxaparin data, the submitted data were insufficient to demonstrate clinical efficacy and support a labeled claim of reversal of anticoagulation for this drug.

Consistent with results from the healthy volunteer studies, these data show that Andexxa can reverse anticoagulation (as measured by anti-FXa activity); however depth of reversal is not sustained once the infusion is complete. As expected, the

submitted data is insufficient to allow for meaningful conclusions to be drawn about efficacy in this population, in terms of correlation between the decrease in anti-FXa activity and achievement of hemostatic efficacy. Since anti-FXa activity has not been shown to correlate with risk of bleeding, the clinical significance of these findings is unclear. These preliminary data show that the depth of reversal is not as robust in patient presenting with supratherapeutic anti-FXa levels, which could result in continued bleeding or evidence of re-bleeding. To date, no subject in this trial had reported re-bleeding; however, the database may not be large enough to capture these events, particularly if the incidence of re-bleeding is low. These data also raise concerns for adequacy of the proposed dosing regimen as mean anti-FXa activity return to higher than 50% of baseline values by the 4 hour assessment; additional dosing or a longer infusion may be warranted. Furthermore, for the 10/12 rivaroxaban subjects treated with the low dose, reversal was variable (-22 to 95% post-bolus and -42 to -91 post-infusion). If you exclude the one subject with supratherapeutic levels, 2/9 (22%) had reductions of <80% post-bolus or post infusion:

- **Subject** (b) (6) **had a baseline level of 389.1 ng/mL with 58% reduction post-bolus, but 87% post-infusion.**
- **Subject** (b) (6) **had a baseline level of 295.2 ng/mL with 98% reduction post-bolus, but only 54% post-infusion.**

For the 2 subjects treated with the high dose, reversal was >95% post-bolus and post-infusion; however, these numbers are too small to make any meaningful conclusions.

In addition, in the absence of control data, the effect of Andexxa on hemostasis cannot be assessed since hemostasis is an expected event even in the absence of reversal or procoagulant therapy in subjects who experience bleeding related to these anti-coagulants, due in part to the short half-life of the anticoagulants. Examples noted during the review in non-visible bleeding types that made the assessment of Andexxa's effect on hemostasis challenging include the a) inability to quantify bleeding b) the absence of ongoing bleeding pre- and post-treatment in some cases, c) study entry based soley on non-specific symptoms and not on signs/ symptoms that relate to intravascular volume loss or overt bleeding d) adjudication issues with the GI bleed assessments as noted in the adjudication reports, and e) the lack of clarity as to how clinical assessments or endoscopy findings would be incorporated into the assessment of hemostasis. Illustrative cases are discussed in section 7.1.7. Due to these difficulties reliably assessing efficacy in these bleeding types, FDA recommended revising the eligible population to ICH to permit hemostasis assessment in more relevant population with regard to mortality and morbidity outcomes where objective measures are utilized in the existing protocol to assess hemostasis. During the meeting between FDA and Portola on July 27, 2016, Portola noted that one of their adjudicators served as Portola's consultant neurologist and leader of (b) (4) **responsible for central reading of the brain imaging studies. The FDA plans to evaluate during the review of the revised**

ANNEXA 4 study the impact of such practices on the ability of the EAC to independently adjudicate efficacy outcomes.

6.3.11.3 Subpopulation Analyses

Analysis of EAP
Of the 23 subjects that comprise the EAP, 18 (78%) subjects were successfully treated with Andexxa.

For rivaroxaban, results from the analysis in the EAP were the same as the primary analysis discussed above.

For apixaban, the EAP includes 11 of the 18 treated subjects, including 1 that was treated for a retroperitoneal bleed, 5 that was treated for a GI bleed, and 5 with ICH. All subjects received the low dose Andexxa regimen (400 mg bolus + 480 mg infusion).

A total of 8/11 (73%) of subjects achieved excellent/good hemostatic efficacy; 2 subjects ((b) (6) and (b) (6)) had a poor response as discussed in section 6.3.11 above and 1 assessment was pending.

The mean baseline anti-FXa activity level for these 11 subjects was 290 ng/mL (SD: 61 ng/mL; median 161.5 ng/mL; range: 91.3 to >950 mg/L). The mean percent change from baseline anti-FXa activity to post infusion was -77%.

The mean anti-FXa activity at four hours post-infusion was 225.2 ng/mL. For the 10 subjects with post-infusion levels at 8 and 12 hours, the mean anti-FXa activity was 209.4 and 173.9 ng/mL, respectively.

Mean unbound levels of apixaban decreased from baseline levels of 23.4 ng/mL to 11.7 ng/mL post-infusion; however, both baseline and post-infusion levels were higher than what was observed in part 2 of the phase 3 study. For the 9 subjects with available data, mean anti-FXa activity levels at 4, 8 and 12 hours were 23, 14.2 and 13.9 ng/mL, respectively.

Reviewer Comment: As previously stated, FDA advised that the primary analysis should be done on the ITT population, and not the EAP because the clinical significance of a level of the 75 ng/ml cut-off in terms of bleeding risk is not known. Furthermore, in the absence of a companion diagnostic to obtain anti-FXa activity in real time it is very likely that if Andexxa is approved patients with anti-FXa activity levels <75 ng/mL will be treated. In fact, 8/35 (23%) of the subjects treated in the confirmatory study had anti-FXa activity levels <75 ng/mL. Therefore the efficacy of the product need to be established for the whole clinical trial population in order to allow for generalizability of these data to the target population.

6.3.12 Safety Analyses

6.3.12.2 Overview of Adverse Events

A total of 16/35 (46%) subjects experienced 35 TEAEs, including one non-serious TEAE of headache which was considered related to Andexxa. No new safety signals were identified.

6.3.12.3 Deaths

The following subjects died while on study:

- Subject (b) (6) was a 95 year-old white female with a history of stroke ((b) (6)), TIA, atrial fibrillation, congestive heart failure, hypertension, hyperlipidemia, and diabetes, who was taking rivaroxaban 15 mg once daily for treatment of atrial fibrillation and presented to the ED with an ICH due to blunt trauma. The subject was assigned the high dose Andexxa regimen and completed the infusion without incident. Approximately 6.5 hours post treatment (SD 2) the subject was found to have hemiplegia and aphasia and MRI evidence of stroke (diffuse acute non-hemorrhagic left anterior frontal cortex infarct and non-hemorrhagic infarct of the caudate). The subject subsequently died (SD13) due to 'subdural hematoma, preceded by stroke.' This death is considered related by this reviewer and the investigator.
- Subject (b) (6) was an 84 year-old white female with a prior medical history of MI, atrial fibrillation, renal failure, COPD, PE, CHF, hypertension, colon cancer, and prior tobacco use, who was taking apixaban 2.5 mg bid for atrial fibrillation and presented to the ED with an intra-articular bleed after a fall at home which fractured her hip and neck vertebrae. The subject was assigned the low dose Andexxa regimen and completed the infusion without incident. On SD 2 the subject the patient was taken to the operating room for fixation of the hip fracture. The procedure was complicated by cardiac arrest, "believed to be due to a previous acute MI" and the subject died on SD 8. The cause of death was 'accident' and was considered unrelated by the investigator. This reviewer agrees that the accident was unrelated Andexxa; however, the acute MI could have been related to Andexxa.
- Subject (b) (6) was an 84 year-old, white female with a history of atrial fibrillation, congestive heart failure, CABG surgery, hypertension, renal dysfunction, and peptic ulcer, who was taking apixaban 2.5 mg bid for atrial fibrillation and presented to the ED with ICH. The subject was assigned the low dose Andexxa regimen and completed the infusion without incident. On SD 17 the subject was transferred from the floor to the ICU with acute hypoxic respiratory failure. The patient was hypotensive and bradycardic, requiring intubation. Cardiopulmonary resuscitation was conducted for 20 minutes before the family requested no further resuscitation. The cause of death was cardiogenic shock, secondary to hypoxia, and acute coronary syndrome and was considered unrelated to Andexxa.

Reviewer Comment: The number of deaths initially reported is <10% (3/35) which on its face do not raise any safety concerns; however, it is difficult to make any general statements about the product's safety since we do not have control rates in a similar population.

6.3.12.4 Nonfatal Serious Adverse Events

Ten subjects experienced 15 SAEs, including one subject ((b) (6)) that had a SAE of ischemic stroke that was considered related to the product. Per the applicant, no other SAEs were considered related to Andexxa.

6.3.12.5 Adverse Events of Special Interest (AESI)

Table 12: Thromoembolic Events

subject ID	Anticoag	Indication	Bleed Site	Andexxa Dose	Thrombotic Event	SD	Investigator Causality	Reviewer Causality	Reanticoagulation (Y/N)
(b) (6)	Rivaroxaban	DVT	GI	High	PE	24	unrelated	unrelated	No
	Apixaban	DVT	Visible	Low	DVT (multiple)	3	unrelated	**related**	No
					DVT (multiple)	11	unrelated	unrelated	No
	Apixaban	Afib	ICH	Low	DVT (L com fem)	28	unrelated	unrelated	No
	Rivaroxaban	Afib	ICH	High	ischemic stroke	2	related	related	No
	Apixaban	Afib	ICH	Low	cardiogenic shock/death	17	unrelated	unrelated	No
	Apixaban	Afib	M/S (intra-articular)	Low	acute MI	2	unrelated	**related**	No
	Enoxaparin	VTE prev	pericardial	High	infarct (L cerebral)	6	unrelated	unrelated	No
					infarct (post fossa)	6	unrelated		
					infarct (right cerebral)	6	unrelated		

Note: This table reflects the thrombotic events reported in the initial submission. In the 180-day safety update a total of 16 thromobotic events were reported in 9 subjects and are discussed in section 8.4.8.

Subject Narratives

- (b) (6) : 76 year-old with history of hypertension, skin cancer, and prior tobacco use, who presented to ED on SD 24 with shortness of breath. The subject was found to have a normal chest radiograph but a VQ scan showed a high probability for PE; Doppler flow studies of the lower extremities showed no evidence of DVT. D-dimer was elevated at 1737 ng/mL (0-499).
- (b) (6) : 57 year-old with history of hypertension and recent DVT who developed SDH 6 hours post-infusion that was not visualized on the screening CT; On SD 3 and SD 11, the subject was found to have multiple DVTs in the lower and upper extremities, which was considered unrelated by the investigator

but related by this reviewer. Although the subject had multiple risk factors, including recent DVT and near complete reversal of anticoagulation with 95% reduction of anti-FXa levels, the occurrence of multiple DVTs within 7 days of Andexxa infusion makes it difficult to rule out any contribution from the drug.

- (b) (6) : 84 year-old with history of atrial fibrillation, hypertension and colon cancer who was readmitted on SD 23 for seizures, UTI and sepsis and was found to have a DVT on ultrasound on SD 28.
- (b) (6) : 95 year-old with history of stroke, TIA, atrial fibrillation, congestive heart failure, hypertension, hyperlipidemia, and diabetes, who developed aphasia and hemiplegia 6.5 hours after the end of Andexxa infusion with MRI evidence of stroke (diffuse acute nonhemorrhagic left anterior frontal cortex infarct and non-hemorrhagic infarct of the caudate). The subject subsequently died (SD13) due to 'subdural hematoma, preceded by stroke.'
- (b) (6) :84 year-old with history of atrial fibrillation, congestive heart failure, CABG surgery, hypertension, renal dysfunction, and peptic ulcer, who developed acute hypoxic respiratory failure (SD 17) with hypotension, bradycardia requiring intubation. Bronchoscopy was negative for mucus plug/obstruction. The subject's blood pressures were unresponsive to vasopressors; resuscitation was discontinued after 20 minutes at the family's request. The cause of death was cardiogenic shock, secondary to hypoxia, and acute coronary syndrome.
- (b) (6) : 84 year-old with history of MI, atrial fibrillation, renal failure and COPD, PE, CHF, hypertension, colon cancer, and prior tobacco, who was taken to the operating room for fixation of the hip fracture on SD 2 and subsequently had cardiac arrest, "believed to be due to a previous acute MI." The subject died on SD 8. Although the subject had multiple risk factors, an association between the thrombotic event and Andexxa administration cannot be ruled out.
- (b) (6) : 70 year-old with history of recent CABG surgery, atrial fibrillation, hypertension, hyperlipidemia, diabetes, and prior tobacco use, who developed right-sided weakness, hemiparesis and numbness (SD 6); MRI showed findings consistent with a stroke (multifocal acute and sub-acute hemorrhagic and nonhemorrhagic infarcts in the right and left cerebral hemispheric and posterior fossa infarcts). The patient was not re-anticoagulated post Andexxa. Several old infarcts were noted to contain punctate areas of petechial microhemorrhage. Bilateral cardioembolic events were deemed more likely than metastatic disease in this patient by the radiologist. MRA showed dilation of the anterior circulation demonstrating evidence of high grade stenosis or arterial occlusion.

Reviewer Comment: The risk of thrombosis cannot be adequately assessed with this safety database because of the limited data provided in the submission and a lack of an adequate control group to understand baseline rates of thrombosis in this population. Additional information with regard to the duration of TFPI inhibition may provide information with regard to the at-risk period following Andexxa infusion. Because of these reported related thrombotic events and the uncertainties of TFPI procoagulant contribution to the mechanism of action of Andexxa, this reviewer recommends the risks of thrombosis be conveyed in a boxed warning in the label if approved. As noted above, monitoring for acute kidney injury was

inadequate as serum chemistries were obtained at baseline only. In response to FDA Question 1c (received on July 8, 2016) Portola stated that "In the Phase 1-3 studies in healthy volunteers and in the > 100 bleeding patients treated in ANNEXA-4, there have been no sensitivity issues that have been specifically linked to the tolerability of sucrose or mannitol." This statement is misleading; although healthy volunteers dosed with andexanet alfa did not develop acute kidney injury, the inadequacy of monitoring in ANNEXA-4 precludes one from making any general conclusions about sucrose-related toxicity. It is unclear how the determination of "no sensitivity issues" was made in the absence of adequate monitoring. ANNEXA-4 needs to be revised to include monitoring for acute kidney injury (e.g., serum chemistries, urine output, etc) at pre-specified time points after the administration of andexanet.

6.3.13 Study Summary and Conclusions

The number of subjects included in the preliminary data submitted is too small to draw meaningful conclusions about safety and efficacy. No new safety signals were identified. Furthermore, the lack of an appropriate control group makes interpretation of these findings difficult. The submitted data were insufficient to adequately assess the correlation between the surrogate endpoint, anti-FXa activity, and hemostatic outcome; however, based on the limited preliminary data submitted, there is uncertainty whether the study as designed will show that anti-FXa is a surrogate endpoint reasonably likely to predict clinical benefit.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The applicant proposed the following indication:

For patients treated with a direct or indirect FXa inhibitor when reversal of anticoagulation is needed in situations such as:

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

However, there were insufficient data to support an indication for indirect FXa inhibitors (e.g., enoxaparin) or edoxaban as reversal of these drugs were not adequately studied in phase 3 studies:
For enoxaparin:

- No phase 3 data are available
- In the study 12-502 (Module 3):
  - 18 subjects received bolus only infusions, including 6/18 that received 420 mg (low) dose. Note: the 420 mg dose was the liquid formulation, which the applicant states corresponds to the 400 mg dose in the lyophyilized form.
  - No subjects received high dose

– No subjects received bolus + infusion

For Edoxaban:

- No phase 3 data are available
- In the study 12-502 (Module 4):
  – 12 subjects received bolus only dosing, of which only 6 received the proposed licensed dose of 800 mg (the remaining 6 received a dose of 600 mg)
  – An additional 6 subjects received a 800 mg bolus + infusion regimen at the proposed infusion rate but only for 1 hr
  – Efficacy data showed that the bolus + infusion regimen used resulted in ~67% reduction in anti-FXa activity (64% for active metabolite).

In addition, there were no data submitted to support the use of this product in (b) (4) settings.

7.1.1 Methods of Integration

An integrated analysis of efficacy is limited by the differences in anticoagulant therapy, Andexxa doses, study designs, and time points of efficacy evaluation. Instead, a summary of relevant efficacy data from 4 studies (14-503, 14-504, 12-502 and 14-506) in healthy subjects and 1 study in bleeding patients that support the limited indication for Andexxa is presented. These studies are summarized in Table 13 below.

Table 13: 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) 20 mg orally every 24 hours for 4 days	n=26 800 mg bolus followed by a 120 min infusion at 8 mg/min	n=13
14-505 Efficacy/ Safety	Multicenter, open-label, single arm	n=35 subjects with acute major bleeding (32 evaluable) 78 years (55–95)	Apixaban (n=18) Rivaroxaban (n=13) Enoxaparin (n=4) Edoxaban (n=0)	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 *Recommended dose is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor*	N/A
Phase 3 subtotal		*N=180*	*N=180*	*N=136*	*N=44*
Phase 2 Study					
12-502 Safety, PK/PD	Single center, randomized, double-blind, vehicle-controlled	n=54 healthy subjects 33 years (19-44)	Module 1: Apixaban (n=54) 5 mg orally every 12 hours for 6 days	N=36 90 mg (n=6) 210 mg (n=6) 420 mg (n=6) 600 mg (n=6) 900 mg (720 mg +4mg/min for 120 min; n=6)	n=18
		n=48[a] healthy subjects 36 years (19-45)	Module 2: Rivaroxaban (n=48) 20 mg orally every 24 hours for 6 days	n=30 210 mg (n=6) 420 mg (n=6) 600 mg (n=6) 600 mg (420 mg +4 mg/min for 45 min; n=6) 900 mg (720 mg +4mg/min for 60 min; n=6) 1760 mg (800 mg +8 mg/min for 120 min; n=6)	n=15

		n=27 healthy subjects 34 (21-45)	Module 3: Enoxaparin (n=27) 40 mg subcutaneously every 24 hours for 6 days	n=18 210 mg bolus (n=12) 420 mg (n=6)	n=9
		n=28[b] healthy subjects 33 (19-45)	Edoxaban (n=28) 60 mg orally every 24 hours for 6 days	n=18 600 mg (n=6) 800 mg (n=6) 1280 mg (800 mg + 8 mg/min for 60 min (n=6)	n=8
Phase 2 subtotal		*N=157*	*N=157*	*102*	*50*
Phase 1 Study					
14-506 Safety, PK/PD	Single center, open-label	n=20 healthy subjects 50 years (26-69)	Apixaban (n=20) 2.5 mg orally every 12 hours for 3.5 days	Group 1 (younger subjects): n=10 400 mg bolus	N/A
				Group 2 (older subjects): n=10 400 mg bolus	
Phase 1 subtotal		*N=20*	*N=20*	*20*	*0*
TOTAL (phase 1, 2, 3/3b)				258	94

PK=Pharmacokinetics; PD=Pharmacodynamics
[a]:45 subjects were enrolled and treated with rivaroxaban; however, 3 subjects were discontinued prior to receiving Andexxa/placebo due to problems with the infusion pumps.
[b]: 2 placebo subjects were discontinued following anticoagulant treatment and prior to placebo treatment.
Source: Adapted from Summary of Clinical Efficacy page 49/159

7.1.2 Demographics and Baseline Characteristics

Table 14: Demographics and Baseline Characteristics (Integrated Analysis)

	Study 14-503		Study 14-504		Study 12-502			Study 14-506[*-]		Study 14-505 (n=32)
	Part 1 (n=33)	Part 2 (n=32)	Part 1 (n=41)	Part 2 (n=39)	Mod 1 (n=54)	Mod 2 (n=48)	Mod 3 (n=27)	Younger (n=10)	Older (n=10)	
Age, years Mean	60.4	59.4	55.2	57.3	33.2	35.8	33.7	33.1	67.4	76.8
Median (range)	59 (50-73)	56.5 (50-73)	55 (50-65)	57 (50-68)	33 (19-44)	37.5 (19-45)	34 (21-45)	32.5 (26-42)	67.5 (65- 69)	79 (55- 95)
Gender, % male female	57.6 42.4	68.8 31.2	63.4 36.6	56.4 43.6	85 15	81	63 37	50 50	50 50	53 47
Race, % White Black/AA	100% -	90.6 6.3	78.0 14.6	71.8 25.6	96 4	90 6	93 7	40 30	50 20	84 16

Asian AI/Alaska Native Other	- -	- -	2.4 - 4.9	2.6 -		- 4 -	- - -	30 - -	30 - -	- - -
Ethnicity, % Hispanic/Latino Non-Hispanic/Latino	42.4 57.6	40.6 59.4	31.7 68.3	35.9 64.1	80 20	79 21	85 15	10 90	10 90	6 94

AA = African American AI=American Indian
*younger=18-45 years; older ≥65 years
Source: Adapted from 125586/0, *Summary of Clinical Efficacy*, page 101/150

Reviewer Comment: In general, treatment groups were balanced with respect to baseline characteristics. Most of the subjects enrolled in the phase 3 clinical trials of Andexxa were older (50-73 years old), but were notably younger than the study population of bleeding patients that is currently enrolled in the confirmatory study. Because advanced age is known to impact bleeding outcomes, these data may not be sufficient to characterize the safety and efficacy of the product in the target population; data in the bleeding population is needed. Likewise, the impact of renal impairment cannot be evaluated at this time as no studies in renally impaired patients were done. The enrolled population of the confirmatory study is an adequate representation of the broader population targeted by the proposed indication. The numbers of patients and racial breakdown are too small to make any meaningful conclusions as to the role of age or race in the treatment of Andexxa. There is no racial or ethnic predilection reported with bleeding outcomes; therefore there is no expectation of different efficacy based on gender or ethnicity.

7.1.4 Analysis of Primary Endpoint(s)

Percentage Change From Baseline in Anti-FXa Activity to the Nadir

Apixaban
Reversal of apixaban was evaluated for efficacy in 122 subjects enrolled in studies 12-502 Module 1, 14-503 Part 1 and Part 2, 14-505 and 14-506. At all doses studied (90 to 900 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. In general, anti-FXa activity returned to placebo levels within 2 hours after completion of administration and for subjects dosed within the therapeutic range in the phase 3 study, Andexxa resulted in >90% reduction in anti-FXa activity. Of the 122 subjects dosed with Andexxa, 46 (38%) subjects were studied with the proposed licensed dose and 42 were considered evaluable:

- Study 12-502 Module 1: Of the 36 subjects dosed with Andexxa in this study, 6 received 420 mg IV followed by a continuous infusion of 480 mg (4 mg/min over 120 minutes (liquid formulation of proposed licensed dose). Following the 420 mg dose, anti-FXa activity decreased by > 93% relative to baseline. An additional 18 subjects received either a 420 mg dose with no infusion (n=6), 420 mg dose with 45 minutes of continuous infusion (n=6), or 420 mg followed by an additional bolus dose of 180 mg, all with comparable degrees of reduction in anti-FXa activity.

- 14-503 Part 2: 24 subjects received 400 mg IV followed by a continuous infusion of 480 mg (4 mg/min over 120 minute). Following the 400 mg dose, anti-FXa activity decreased immediately by >90% relative to baseline. An additional 24 subjects received the bolus 400 mg dose only with comparable degrees of reduction in anti-FXa activity.
- 14-505: 18 subjects were enrolled and treated, of which 16 (89%) had major bleeds; one subject's efficacy analysis was pending and an additional subject had baseline anti-FXa activity that was <4 ng/mL. This reviewer included 12 subjects in the evaluable population as two subjects ((b) (6) and (b) (6)) had bleeds that were considered not evaluable by the EAC. The mean percent change from baseline anti-FXa activity to post-bolus was -84%. For the 11 subjects with available data, the mean percent change from baseline anti-FXa activity to post-infusion was -77%.
- 14-506: No subjects received the proposed licensed dose; however 20 subjects received a 400 mg IV bolus that resulted in a 93% reduction in the younger cohort and 89% in the older cohort.

Reviewer Comment: As noted in in section 6.3.11, for three subjects enrolled in 14-505 with higher baseline anti-FXa values, the percent reduction after the infusion was <50%. Exclusion of these data results in a similar percent change from baseline of >90% (both post-bolus and post-infusion) suggesting that for life-threatening bleeds that occur within the therapeutic range, Andexxa is capable of significantly reducing anti-FXa. However, for bleeds associated with supratherapeutic levels, additional dosing or a longer infusion may be required.

This is a very limited database to evaluate efficacy of the proposed dose. If you consider that the pattern of reversal has been consistent in that the depth of reversal is determined by the bolus dose and subsequently maintained by the continuous infusion, one could extrapolate efficacy and include data from subjects dosed with only the bolus dose regimen, which would increase the efficacy database to 108 subjects (104 evaluable). Although limited, these data were considered sufficient for establishing that the proposed low dose Andexxa can reverse anticoagulation of apixaban for up to two hours post-infusion.

Rivaroxaban

Reversal of rivaroxaban was evaluated for efficacy in 96 subjects enrolled in studies 12-502 Module 2 (n=30), 14-504 Part 1 and Part 2 (n=53), and 14-505 (n=13). At all doses studied (210 to 1760 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. Of the 95 subjects dosed with Andexxa, only 44 subjects were studied with the proposed licensed dose and considered evaluable. For subjects in the phase 3 study, anti-FXa activity returned to placebo levels within 2 hours after completion of administration and for subjects dosed within the therapeutic range in the phase 3 study, Andexxa resulted in >90% reduction in anti-FXa activity.

- Study 12-502 Module 2: Of the 30 subjects dosed with Andexxa in this study, 6 received 800 mg IV followed by a continuous infusion of 960 mg (8 mg/min over 120 minutes. Following the 800 mg dose, anti-FXa activity decreased immediately by > 90% relative to baseline. An additional 6 subjects received a 420 mg bolus dose and reduction in anti-FXa activity was considerably lower at -51%. Please see section 6.2.4 for a discussion of the dose dependent nature of reversal for Rivaroxaban.
- 14-504 Part 2: 26 subjects received 800 mg IV followed by a continuous infusion of 960 mg (8 mg/min over 120 minute). Following the 800 mg dose, anti-FXa activity decreased immediately by > 90% relative to baseline. An additional 27 subjects received the bolus 800 mg dose only with comparable degrees of reduction in anti-FXa activity.
- 14-505: 13 subjects were enrolled and treated, of which 12 had major bleeds. The mean percent change from baseline anti-FXa activity to post-bolus and post-infusion was -81% and -79%, respectively.

Reviewer Comment: As noted in in section 6.3.11, 1 subject had baseline levels that were ≥2 SD above the mean from the phase 3, part 2 study, with resulting post-bolus and post-infusion levels of 52% and 44%, respectively; exclusion of these data results in a percent change from baseline of >80% (both post-bolus and post-infusion). As discussed previously, the results for rivaroxaban are not as consistent as with apixaban in that a wide range of reversal for bleeding events within therapeutic range is noted with the proposed low dose regimen. Consideration of the phase 2 data that demonstrated <80% reduction with the 420 mg bolus dose and the lack of phase 3 data demonstrating consistent reversal precludes further consideration of including the low dose as a labeled dosing regimen for rivaroxaban.

Hemostatic Efficacy

Hemostatic efficacy was evaluated only in the confirmatory study (and not healthy volunteer studies) and is discussed in section 6.3.11. Because of the dosing concerns and limited duration of effect as evidenced by the return of anti-FXa activity to >50% of baseline values by the 4-hour assessment time-point, additional analysis was done to evaluate hemostatic efficacy for subjects with ICH where clinical guidelines recommend reversal of anticoagulation for at least 24 hours (discussed in 7.1.7 below). These efficacy analyses were considered supportive analyses as the regulatory decision for efficacy was based on the healthy volunteer data reviewed under accelerated approval regulations, as advised by CBER management.

7.1.7 Subpopulations

GI bleeds

Sixteen subjects with GI bleeds were enrolled: 6 subjects on apixaban, 8 subjects on rivaroxaban and 2 subjects on enoxaparin. Subject (b) (6) (apixaban) was excluded by this reviewer because the baseline anti-FXa activity level was <4 ng/mL and subject (b) (6) (rivaroxaban) had a bleed that was not considered major.

For the 12 remaining subjects treated with apixaban or rivaroxaban, the mean baseline anti-FXa activity levels were 337 ng/mL. Treatment with Andexxa resulted in 81% reduction in anti-FXa activity levels post-bolus and 71% reduction post-infusion. Based on the EAC's adjudication, a total of 11/12 (92%) received a rating of excellent/good and 1 (subject (b) (6)) received poor/none.

However, as noted previously, FDA was unable to confirm these successful adjudications for the following reasons:

1. At least two subjects did not meet eligibility criteria of having an acute major or life-threatening GI bleed:
    - Subject (b) (6) was a 67 year-old male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with bright red blood per rectum, without evidence of hemodynamic compromise, significant anemia (hemoglobin was maintained at > 8 g/dL and no drop of more than 2 g/dL was noted). Two of five adjudicators considered this subject ineligible for study entry.
    - Subject (b) (6) , a 77 year-old African-American female patient taking rivaroxaban 20 mg once daily for VTE prevention, presented to the ED with shortness of breath while walking and anemia (hemoglobin 5.5 g/dL) without documentation of active bleeding. Two adjudicators indicated that the evidence pointed to continued bleeding and one indicated that there was insufficient evidence for acute bleeding.
      Note: eligibility for subject (b) (6) *, a 70 year old female with a history of an ejection fraction of 15% taking rivaroxaban 20 mg once daily for atrial fibrillation who was reported to have decreased blood pressure (81/42), poor skin perfusion, and increased creatinine in the setting of a normal hemoglobin of 13.5 g/dL that remained stable in the absence of any blood transfusions (12-hour post-infusion hemoglobin was 12.6 g/dL) was also considered questionable by the review team.*

2. Adjudication of hemostatic efficacy was inconsistent with clinical findings for two subjects:
    - Subject (b) (6) , an 81 year-old African-American male taking apixaban 5 mg twice daily for history of pulmonary embolism, presented to the ED with rectal bleeding. At screening, prior to dosing with Andexxa, his hemoglobin was 7.3 g/dL, creatinine 1.6 mg/dL, and BUN 36.0 mg/dL. Blood pressure and heart rate were normal [107/53 mmHg and 19 beats per minute (bpm)] but the sponsor states "skin perfusion suggested there was evidence of hemodynamic compromise." The subject required one packed red blood cell transfusion prior to receiving low dose of Andexxa, and also required three additional transfusions within the 12 hour post-infusion assessment period. Upper GI and endoscopy results done 12 hours post-dose indicated prescence of a malignant tumor in the gastric fundus and gastric body. Despite this, the EAC adjudicated the hemostatic outcome as successful (rated "Excellent").

      Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	154	8.3	127.1	137.7	130.1

- Subject (b) (6) , a 60 year-old African-American male taking rivaroxaban 15 mg twice daily for VTE treatment, presented to the ED with GI bleeding. At screening, prior to dosing with Andexxa, his hemoglobin was 6.3 g/dL, creatinine 0.7 mg/dL, and BUN 26.0 mg/dL. He received one packed red blood cell transfusion prior to receiving low dose of Andexxa, and also required one additional transfusion and 1 liter of Ringer's solution within the 12 hour post-infusion assessment period. An esophagogastroduodenoscopy report done 10 hours post-infusion showed "diffuse oozing in the stromach from no discernible ulcerations." Despite this, the EAC adjudicated the hemostatic outcome as successful (rated "Excellent").

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	161.2	21.9	88	Not done/reported	45.8

Reviewer Comment: It is unlikely that for these two cases the findings of continued bleeding were considered when the efficacy assessments were made as the adjudication charter does not specify how bleeding events with endoscopic results are to be adjudicated.

3. Hemostatic efficacy could not be determined for three subjects:
   - Subject (b) (6) , a 66 year-old white male taking apixaban 5 mg twice daily for atrial fibrillation, presented with melena and reported hemodynamic compromise (blood pressure of 91/56 mmHg and heart rate of 87 bpm), which all resolved prior to Andexxa treatment; melena was not noted pre-bolus or thereafter. Despite this, the EAC adjudicated the hemostatic outcome as successful (rated "Good") based on the fact that the 12-hour hemoglobin did not drop more than 20%.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12

Anti-FXa activity (ng/mL)	263.4	36.3	166.9	182.9	174.6

- Subject (b) (6) , a 76 year-old white female taking rivaroxaban 20 mg once daily for VTE prevention, presented with hematemesis that appear to have resolved prior to Andexxa treatment. Despite this, the EAC adjudicated the hemostatic outcome as successful (rated "Excellent").

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	160.9	<4	Not done/reported	38.1	54.7

- Subject (b) (6) , a 63 year-old African-American male, taking rivaroxaban 15 mg twice daily for VTE treatment, presented to the ED with an upper GI bleed and melena that resolved prior to Andexxa treatment. Despite this, the EAC adjudicated the hemostatic outcome as successful (rated "Excellent").

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	152.8	14.5	90	70.6	53.9

Reviewer Comment: These examples show how the assessment of Andexxa's effect on hemostasis is challenging for non-visible bleeding, and for GI bleeding in particular. If these preliminary data are illustrative of the enrolled population that will serve as the basis for approval, the study will have a very small number of evaluable subjects with interpretable data. As noted previously, while several changes to the protocol could address the issues of not being able to quantify bleeding and not having documentation of ongoing bleeding pre- and post-treatment, and improve the study entry criteria to ensure that documentation based solely on non-specific symptoms is avoided, a study in ICH would provide a more interpretable database to evaluate safety and efficacy of Andexxa.

ICH

Thirteen subjects with ICH were enrolled, of which 12 were considered to have a major bleed and 11 had available efficacy ratings. An additional subject ((b) (6)) was excluded because this subject received two platelet transfusions within 3 hours of completing the Andexxa infusion; the platelet contribution to the hemostatic process confounds the assessment of efficacy in this case. Subjects with CT assessments done

more than 2 hours after the pre-specified 12-hour scheduled efficacy assessment were excluded from the analysis; as a result, an additional subject ((b) (6)) was excluded.

For the 9 remaining subjects, mean baseline anti-FXa activity levels were 168.8 ng/mL. Treatment with Andexxa resulted in 94% reduction in levels post-bolus and 91% reduction post-infusion. A total of 6/9 (67%) received a rating of excellent/good and 3 received poor/none.

Subject Narratives

- Subject (b) (6) was a 95 year-old white female, taking rivaroxaban 15 mg once daily for treatment of atrial fibrillation, who presented to the ED with complaints of headache and a CT-confirmed acute subdural hematoma (SDH) due to blunt trauma. The subject was assigned to high dose Andexxa and completed the 800 mg bolus/960 mg infusion without incident. Anti-FXa levels were reduced by 98% following the Andexxa infusion, which was followed by a return of anti-Xa levels to about 60% of the baseline value (see table below). The 1-hour post-Andexxa infusion showed a significant increase in volume; however the increase in thickness was <20% (see table below). At 6.5 hours after the end of the Andexxa infusion, the subject was noted to have hemiplegia and aphasia. A MRI scan done approximately 10 hours post-Andexxa infusion showed a significant increase in thickness from the prior CT evaluation (12.44 mm on CT to 37.02 mm). Comments on the adjudication form state "T2*GRE Images (considering blooming effect)". On MRI scan (done approximately 10 hours after the Andexxa infusion and 12 minutes after the 10 hour CT in the table below) evidence of stroke was confirmed, where "diffuse acute nonhemorrhagic left anterior frontal cortex infarct and nonhemorrhagic infarct of the caudate head were found." The 12-hour post-Andexxa infusion CT scan showed reduced thickness to 11.5 mm. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Excellent' based on serial CT scans. The subject was transferred to hospice care on study day (SD) 5 and subsequently died on SD 13. The cause of death was SDH, preceded by stroke.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	362.3	7.8	212	148	91.6

CT/MRI Scan Findings

	Baseline	Post-Infusion (hours)			
		1-2 hours	7-8	10*	12
Volume (cc)	17.03	22.8	19.65	19.01	16.96
Thickness (mm)	12.8	13.49	12.44	37.02	11.5

*=MRI result

- Subject (b) (6) was an 81 year-old white male patient taking rivaroxaban 20 mg once daily for atrial fibrillation in the intensive care unit (ICU) who had a CT and MRI-confirmed intraparenchymal bleed. The subject was assigned to low dose Andexxa and completed the 400 mg bolus/480 mg infusion without incident. Anti-FXa levels were reduced by 85% following the Andexxa infusion.
- Subject (b) (6) was an 84 year-old, white female taking apixaban 2.5 mg bid for atrial fibrillation who presented to the ED with a CT-confirmed intraparenchymal bleed. The subject was assigned to low dose Andexxa and completed the infusion without incident. Anti-FXa levels were reduced by 95% following the Andexxa infusion.

  Both subjects developed an interim development of intraventricular hemorrhage that was noted after the 1 hour post-infusion assessment and was not documented at baseline. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Good' for Subject (b) (6) and 'Poor/none' for Subject (b) (6).

Anti-FXa Levels

Subject	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
(b) (6)	134.7	20.1	96.8	103	104.3
	117.7	5.8	64	89.8	86.5

CT scan Findings

Subject	Baseline	Post-Infusion (hours)			
		1-2	7-8	12	18
(b) (6)	0.91 cc	1.26 (total 2 cc)	1.49 (4.1 total)	1.31 (1.91 total)	
	2.03	2.31 (2.98 total)		2.31(2.89)	2.34 (3.21)

Reviewer Comment: For subjects (b) (6) and (b) (6), both had intraparenchymal bleeds on baseline CT but were found to have intraventricular hemorrhage (IVH) on follow-up imaging, resulting in higher than baseline total bleed volumes. The applicant stated that for subject (b) (6), "Initially two adjudicators did not consider the ventricular extension as clinically significant in the assessment of hemostatic efficacy. However at the time of committee discussion, Dr. Demchuk, a neurologist, indicated that this should be considered and the committee agreed. Based on that, the committee decision was that the hematoma had expanded > 20%. The issue of intracerebral bleeds that include ventricular hematoma will be raised at the next Adjudication Committee meeting (27 May 2016) for discussion of whether the charter should be amended to specify how such bleeds should be assessed." For subject (b) (6), the applicant stated that "the adjudicators reviewed this case independently and arrived at different conclusions about the case and it was then brought to the committee discussion (as per the Adjudication charter for the first 10-15 cases) where a consensus was reached that the hemostatic response was 'good.' The protocol will need to be revised to specify how these intracranial bleeds are read and adjudicated.

- Subject (b) (6) was an 84 year-old white female taking apixaban 2.5 twice daily for atrial fibrillation who presented to the ED with a reported SDH, mild subarachnoid hemorrhage (SAH), and hemodynamic compromise (based on a blood pressure of 106/58 mmHg, heart rate of 95 beats per minute) and mental confusion. The subject was assigned to low dose Andexxa. Resolution of the mental confusion was noted by the end of the infusion. Anti-FXa levels were reduced by 95% following the Andexxa infusion. Note: none of the study imaging reports document the SAH. This patient had a CT scan done 14 hours before study enrollment that showed a SDH. The initial study CT was done 53 minutes after the bolus dose of Andexxa was administered, but subsequent imaging showed no significant increase in thickness or volume during the 12 hours post-infusion. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Excellent'.

  However, a repeat CT done approximately 13 hours after the Andexxa infusion showed significant increases in volume and thickness of the SDH with no midline shift. The following day, SD 3, the subject experienced serious adverse event of seizures. Electroencephalography showed 3 left temporal seizures. There were 17 left temporal seizures with similar interpretation for which the subject was treated with several doses of valproic acid and then lacosamide. These findings were considered consistent with an "acute insult and focal disturbance of cerebral function." A neurologist's evaluation concluded: Complex Partial Status, improved, and secondary to SDH, SAH. The subject was discharged to a

nursing home and was subsequently readmitted on SD 28 with a left femoral vein deep vein thrombosis (DVT). The patient was treated with enoxaparin 30 mg once daily on SD 3 through SD 30.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	91.3	4.2	23.6	42.2	39.6

CT scan Findings

	Post-Bolus	Post-Infusion (hours)		
		3	12	13
Volume (cc)	26.1	23.7	18.72	29.6
Thickness (mm)	1.23	1.3	1.2	12

Reviewer Comment: In an information request, the applicant clarified that there was an error in the (b) (4) evaluation in that the earlier measurements were given in centimeters not millimeters (e.g., 1.23 instead of 12. 3 mm). Thus there was no significant increase in hematoma thickness.

- Subject (b) (6) was a 90 year-old white male taking rivaroxaban 20 mg once daily for atrial fibrillation who presented to the ED with a SDH due to blunt trauma. The subject was assigned to low dose Andexxa. Anti-FXa levels were reduced by 83% following the Andexxa infusion. The 1-hour post-infusion CT showed a significant increase in thickness from 12.23 mm at baseline to 21 mm. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Poor/none.' The subject was discharged from the hospital on SD 3 and re-anticoagulated with rivaroxaban, 20 mg once daily.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	176.1	30.6	122.6	90.5	50.8

CT scan Findings

	Baseline	Post-Infusion (hours)

		1-2	12	28
Volume (cc)	14.32	26.71	25.84	17.73
Thickness (mm)	12.23	21	20.2	17.47

- Subject (b) (6) was an 85 year-old white female taking apixaban 5 mg twice daily for atrial fibrillation who was assigned to low dose Andexxa for a CT-proven SDH. Anti-FXa levels were reduced by 90% following the Andexxa infusion. The 1-hour post-infusion CT showed an increase in thickness from 8.2 mm at baseline to 10.8 mm, which was >20% but ≤35%. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Good.' The subject was discharged from the hospital on SD 3 and was not re-anticoagulated.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	191.6	19.5	129.8	138.6	112.5

CT scan Findings

	Baseline	Post-Infusion (hours)	
		1-2	12
Volume (cc)	58.43	59.32	41.77
Thickness (mm)	8.2	10.8	10.84

- Subject (b) (6) was a 77 year-old white male taking rivaroxaban 15 mg once daily for atrial fibrillation who presented to the ED with a CT-proven SDH. The subject was assigned to low dose Andexxa. Anti-FXa levels were reduced by 89% following the Andexxa infusion. Follow-up imaging showed stable or decreased thickness; however, the increase in volume was >20% at the 1-hour post-infusion assessment. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Excellent.' The subject was discharged from the hospital on SD 2 and was not re-anticoagulated.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)

		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	218.5	23.7	121.7	125.5	95.9

CT scan Findings

	Baseline	Post-Infusion (hours)	
		1-2	12
Volume (cc)	21.23	26.28	19.93
Thickness (mm)	0.89	0.92	0.75

- Subject (b) (6) was an 84 year-old white male taking apixaban 5 mg twice daily for atrial fibrillation and VTE prevention who presented to the ED with a CT-proven cerebellar hemorrhage. The subject was assigned to low dose Andexxa. Anti-FXa levels were reduced by 91% following the Andexxa infusion. Follow-up imaging showed increased volume at the 1-hour and 12-hour post-infusion assessments, as compared to baseline. Based on the protocol criteria, the adjudication committee assessed hemostatic efficacy as 'Good.' The subject was discharged from the hospital on SD 3 and was not re-anticoagulated.

Anti-FXa Levels

	Baseline	Post-Infusion (hours)			
		End of Infusion	4	8	12
Anti-FXa activity (ng/mL)	161.5	14.8	114.3	131.7	116

CT scan Findings

	Baseline	Post-Infusion (hours)	
		1-2	12
Volume (cc)	1.13	1.77	1.38

Reviewer Comment: Given the heterogeneity in the eligible population (with regard to location and size of the bleed) and the limited number of subjects treated, meaningful conclusions about Andexxa's efficacy in ICH cannot be made. Furthermore, the lack of a control group is problematic for understanding the clinical significance of a success rate of 67%. As discussed previously, Portola committed to conducting a usual care cohort study to serve as a concurrent control. More importantly, changes to the protocol (including revisions to the adjudication

process, possibly additional endpoints, and the institution of clearly defined imaging protocols) are needed to ensure for more interpretable data. SGE neurologist advised that "While it would be preferable to have a more prolonged deep decline in anti-FXa, the 2+ hour decline is probably adequate since most hematoma enlargement associated with neurologic deterioration occurs in the first few hours after bleeding onset" and that based on the available data from the confirmatory study, "there is little evidence that bleeding has continued/recurred after the Andexxa infusion, attesting to the adequacy of the observed decline…When evaluating a treatment intended to stop further bleeding in these patients, it would be much more likely to see a beneficial effect if it is given very early after bleeding onset, and failure to include such patients in trials of pro-coagulant drugs has been one explanation for their failure to translate to clinical benefit in trials to date." FDA CDER DNP consultant views were consistent, stating "It is plausible that adequate hemostasis could occur within two hours of anticoagulant reversal with a resulting reduction in the extent of the injury" but also noting that "procoagulant drugs given acutely have not proven to be beneficial in the past."

Because of the limitations of these data, and concerns about the adequacy of the observed duration of reversal in this particular patient population, this reviewer believes that, if approved, the label should clearly describe the limitations of use for clinical situations where prolonged reversal (>2 hours) is warranted. As **suggested by the neurology consult opinion, the duration of reversal based on nadir anti-FXa levels noted following bolus and infusion with the data available, may be of utility in subjects with ICH if utilized during a time period at which the highest risk of bleeding exists (within the first 3 hours of initial ICH). As previously noted, routine monitoring of anti-FXa levels is currently not done in clinical practice and the ability to obtain these results in 'real time' is variable from center to center.**

7.1.11 Efficacy Conclusions

The efficacy of Andexxa for a limited indication of reversal of direct FXa inhibitors apixaban and rivaroxaban in life-threatening or uncontrolled bleeding has been demonstrated by data from healthy volunteer studies demonstrating that Andexxa can effectively reverse anticoagulation for the duration of the infusion as evidenced by reduction in anti-FXa activity. These conclusions were supported in part by preliminary data from the confirmatory study, which demonstrated that for bleeds in the therapeutic range, Andexxa can effectively reverse anticoagulation as noted by reduction in anti-FXa levels. However, the adequacy of the surrogate to correlate with bleeding outcomes cannot be determined with these limited data.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The safety concerns for this product are hypersensitivity and allergic reactions, thromboembolic events, inhibitor development, and development of antibodies against CHO (b) (4) . Clinical trials evaluated the safety of Andexxa based on AEs,

vital signs, electrocardiograms (ECGs), clinical laboratory evaluations, physical examinations, and assessment of immunogenicity.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Data from 4 of the 5 completed clinical studies are included in the pooled safety analyses:

- Study 14-506: open-label Phase 1 study to compare the safety, PK and PD of Andexxa between older and younger subjects dosed with apixaban.
- Study 12-502: a Phase 2 randomized, double-blind, placebo-controlled, dose-ranging study to assess the safety, tolerability, PK, and PD of Andexxa in combination with one of four FXa inhibitors as separate Modules: apixaban (Module 1), rivaroxaban (Module 2), enoxaparin (Module 3), and edoxaban (Module 4).
- Studies 14-503 and 14-504: single center, randomized, double-blind, placebo-controlled studies designed to confirm the safety and efficacy of the proposed commercial doses for apixaban (14-503) and rivaroxaban (14-504).

Other studies in the Andexxa development program that were not pooled for analysis include:

- Study 11-501: a single center, randomized, double-blind, placebo-controlled, single ascending dose study to assess the safety, tolerability, PK, and pharmacodynamics of Andexxa administered alone.
- Study 14-505: ongoing confirmatory study of acute bleeding patients on FXa inhibitors. These data are discussed separately and includes 57 subjects that were reported in the safety update.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 15 summarizes the subjects treated in completed studies of Andexxa:

Table 15: Summary of Subjects in Completed Studies

Type of Study	Enrolled Subjects (n)	Subjects Administered Anticoagulant (n)	Subjects Administered Placebo (n)	Subjects Administered Andexxa (n)
Phase 3	148	148	44	101
Phase 2	157	154	50	102
Phase 1 (14-506)	20	20	0	20
Phase 1 (11-501)	32	0	8	24
Total	357	322	102	247

Source: Summary of Clinical Safety page 17/173

Table 16 summarizes the healthy volunteer studies in which subjects were anticoagulated with FXa inhibitor and then given Andexxa.

Table 16: Number of Healthy Volunteer Subjects in Clinical Trials of Andexxa

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion					
	400-420 mg (N=62)	**600-800 mg** (N=51)	**Combined Bolus Only** (N=113)	**400-420 mg plus Infusion** (N=36)	**720-800 mg plus Infusion** (N=44)	**Combined Bolus plus Infusion** (N=80)	**Pooled [1] All Doses** (N=223) [a]	**Pooled Placebo** (N=94)	**TOTAL**
Study 12-502									
12-502 Module 1	6	6	12	12		12	36	18	**54**
12-502 Module 2	6	6	12		12	12	30	15	**45**
12-502 Module 3	6		6				18	9	**27**
12-502 Module 4		12	12		6	6	18	8	**26**
Study 14-503									
14-503 Part 1	24		24				24	9	**33**
14-503 Part 2			0	24		24	24	8	**32**
Study 14-504									
14-504 Part 1		27	27				27	14	**41**
14-504 Part 2			0		26	26	26	13	**39**
Study 14-506	20		20				20	0	**20**
TOTAL	**62**	**51**	**113**	**36**	**44**	**80**	**223**	**94**	**317**

[1] Note: The column for all andexanet doses include 30 subjects who received a bolus dose of andexanet of 90, or 210 mg.

[a] Study 11-501 (N=24 administered andexanet; N=8 placebo) was not pooled as discussed in Section 2.7.4.1.1.2.4.4.

Source: ISS Table 3.

Source: Summary of Clinical Safety page 24/173

Table 17 summarizes the demographics of the 223 subjects included in the pooled safety analysis.

Table 17: Demographic Characteristics in the Pooled Safety Analysis

	Andexanet Bolus Only			Andexanet Bolus Plus Infusion				
	400-420 mg (N=62)	**600-800 mg** (N=51)	**Combined Bolus Only** (N=113)	**400-420 mg plus Infusion** (N=36)	**720-800 mg plus Infusion** (N=44)	**Combined Bolus plus Infusion** (N=80)	**Pooled Andexanet All Doses** (N=223)[a]	**Pooled Placebo** (N=94)
Sex, n (%)								
Male	40 (64.5%)	30 (58.8%)	70 (61.9%)	26 (72.2%)	31 (70.5%)	57 (71.3%)	151 (67.7%)	66 (70.2%)
Female	22 (35.5%)	21 (41.2%)	43 (38.1%)	10 (27.8%)	13 (29.5%)	23 (28.8%)	72 (32.3%)	28 (29.8%)
Age, years								
Mean	49.7	46.0	48.0	50.2	47.2	48.6	46.4	45.2
Standard Deviation	15.84	11.92	14.26	15.33	13.18	14.17	14.22	13.18
Median	53.5	50.0	51.0	53.5	52.5	53.0	45.0	44.0
Minimum, Maximum	23, 73	21, 65	21, 73	21, 73	21, 68	21, 73	19, 73	19, 70
Race, n (%)								
American Indian/Alaska Native	1 (1.6%)	1 (2.0%)	2 (1.8%)	0	2 (4.5%)	2 (2.5%)	4 (1.8%)	0
Asian	6 (9.7%)	0	6 (5.3%)	1 (2.8%)	2 (4.5%)	3 (3.8%)	9 (4.0%)	1 (1.1%)
Black or African American	7 (11.3%)	6 (11.8%)	13 (11.5%)	2 (5.6%)	7 (15.9%)	9 (11.3%)	24 (10.8%)	8 (8.5%)
White	48 (77.4%)	43 (84.3%)	91 (80.5%)	33 (91.7%)	32 (72.7%)	65 (81.3%)	184 (82.5%)	84 (89.4%)
Other	0	1 (2.0%)	1 (0.9%)	0	0	0	1 (0.4%)	1 (1.1%)
Ethnicity, n (%)								
Hispanic or Latino	25 (40.3%)	29 (56.9%)	54 (47.8%)	21 (58.3%)	21 (47.7%)	42 (52.5%)	122 (54.7%)	53 (56.4%)
Not Hispanic or Latino	37 (59.7%)	22 (43.1%)	59 (52.2%)	15 (41.7%)	23 (52.3%)	38 (47.5%)	101 (45.3%)	41 (43.6%)

[a] Study 11-501 (N=24 administered andexanet; N=8 placebo) was not pooled as discussed in Section 2.7.4.1.1.2.4.4.

Source: ISS Table 2.

Source: Summary of Clinical Safety page 39-40/173

Table 18: Demographic Characteristics in the Confirmatory Study (14-505)

	FXa Inhibitor n (%)[b]			Total receiving Andexxa[a]
	Rivaroxaban	Apixaban	Enoxaparin	
Total subjects	24 (42.1)	27 (47.4)	6 (10.5)	57 (100)
Male	13 (22.8)	11 (19.3)	4 (7.0)	28 (49.1)
Female	11 (19.3)	16 (28.1)	2 (3.5)	29 (50.9)

Race / Age				
White	17 (29.8)	25(43.9)	4 (7.0)	46 (80.7)
Black	7 (12.3)	2 (3.5)	2 (3.5)	11 (19.3)
Age range (years)	47-95	57-90	55-80	47-95
Mean age (years)	76.3	80.7	67.3	77.1
Type of Bleeding at Randomization				
GI Bleed	14 (24.6)	9 (15.8)	3 (5.3)	26 (45.6)
ICH/Subdural Hematoma	8(14.0)	14 (24.6)	1 (1.8)	23 (40.4)
Musculoskeletal/Visible[c]	1 (1.8)	2 (3.5)	0	3 (5.3)
Other/Nonvisible, n (%)	1 (1.8)	2 (3.5)	2 (3.5)	5 (8.8)

a The Safety Population consisted of 57 subjects who were randomized and received Andexxa with evaluable data.
b Percentages calculated from the number of subjects in the Safety Population.
c Categories of musculoskeletal, nonvisible, and visible were combined in this row.

Source: Summary of Clinical Safety page 41/173

8.2.3 Categorization of Adverse Events

AEs were coded by using MedDRA. The Safety Analysis Population consisted of all subjects randomized and treated with study drug (Andexxa or placebo). Causality was defined as related or unrelated. AEs were considered as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product whether or not the event is considered causally related to the use of the product.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Trial objectives and populations studied were not identical, which limits the ability to do a pooled analysis. As noted above, the phase 1 study 11-501 was of Andexxa alone and therefore was not appropriate to be pooled with studies of anticoagulated subjects. The confirmatory study and healthy volunteer studies were not pooled as the study populations are different (bleeding patients in the confirmatory study vs. healthy volunteers).

8.4 Safety Results

8.4.1 Deaths

All deaths occurred in the confirmatory study and are summarized in Table 18 below:

Table 19: Reported Causes of Death in Study 14-505

Patient ID	Cause of Death	Study Day	Relationship to Study Drug
Apixaban			
(b) (6)	Pneumonia Respiratory failure	21 21	Unrelated
	Cardiogenic shock	21	Unrelated
	Cardiopulmonary arrest	18	Unrelated

(b) (6)	Cardiogenic shock	17	Unrelated
	Unspecified accident	8	Unrelated
Rivaroxaban			
(b) (6)	ICH	1	Unrelated
	Ischemic stroke (SD 2)	13	Related
	Subdural empyema	7	Unrelated

8.4.2 Nonfatal Serious Adverse Events

A total of 20 subjects had SAEs during clinical trials of Andexxa including 1 report of bilateral pneumonia and 1 report of a chemical pregnancy in study 11-501. Of the 57 patients in the safety population of the confirmatory study, 37 SAEs were reported in 18 subjects:

Table 20: SAEs in the Confirmatory Study (14-505)

Pt ID	fXa Inhibitor	Sex	Age	Verbatim Term	Onset (SD)	Serious	Related	Severity	Outcome
(b) (6)	Apixaban	F	74	Mucus plug	9	Yes	Unlikely	Severe	Recovered
	Rivaroxaban	M	60	Melena	6	Yes	Unrelated	Moderate	Recovered
	Rivaroxaban	M	80	Intracerebral hemorrhage	1	Yes	Unrelated	Fatal	Fatal
	Rivaroxaban	F	76	Pulmonary embolism	24	Yes	Unrelated	Severe	Recovered
				Exacerbation of COPD	40	Yes	Unrelated	Severe	Recovered
	Apixaban	F	87	Respiratory failure	21	Yes	Unrelated	Fatal	Fatal
				Pneumonia	21	Yes	Unrelated	Fatal	Fatal
	Apixaban	F	84	Hypoxemic respiratory failure	9	Yes	Unlikely	Severe	Recovered
	Apixaban	M	57	Subdural hematoma	1	Yes	Unrelated	Moderate	Not recovered
				Heparin induced thrombocyte-penia	15	Yes	Unrelated	Mild	Recovered
	Apixaban	F	84	Seizures	2	Yes	Unrelated	Moderate	Recovered with sequelae
	Rivaroxaban	M	73	Subdural empyema	7	Yes	Unrelated	Fatal	Fatal
	Rivaroxaban	M	90	Cellulitis	32	Yes	Unrelated	Severe	Recovered
	Apixaban	M	73	Headache	17	Yes	Unrelated	Severe	Recovered
	Rivaroxaban	F	95	Ischemic stroke	2	Yes	Probable	Fatal	Fatal
	Apixaban	F	88	Cardiogenic shock	21	Yes	Unrelated	Fatal	Fatal
				Pneumonia	19	Yes	Unrelated	Severe	Ongoing (persistent)
				Syncope	19	Yes	Unrelated	Severe	Ongoing (persistent)
				Pulmonary Emboli	21	Yes	Unrelated	Severe	Ongoing (persistent)
				Shock liver	21	Yes	Unrelated	Severe	Ongoing (persistent)
				Bilateral lower extremity DVTs	21	Yes	Unrelated	Severe	Ongoing (persistent)
				Right atrial thrombus	21	Yes	Unrelated	Life Threatening	Ongoing (persistent)
	Rivaroxaban	F	85	Acute on chronic congestive heart failure	17	Yes	Unrelated	Severe	Recovered
				Acute hypoxic respiratory failure	19	Yes	Unrelated	Severe	Recovered
				Sepsis	19	Yes	Unrelated	Severe	Recovered

Source: Summary of Clinical Safety page 120/173

8.4.3 Study Dropouts/Discontinuations

Table 21: Study Disposition in Healthy Volunteer Studies

	Andexanet -- Bolus Only			Andexanet -- Bolus Plus Infusion			Pooled Andexanet All Doses (N=223) [c] n (%)	Pooled Placebo (N=94) n (%)
	400-420 mg (N=62) n (%)	600-800 mg (N=51) n (%)	Combined Bolus Only (N=113) n (%)	400-420 mg plus Infusion (N=36) n (%)	720-800 mg plus Infusion (N=44) n (%)	Combined Bolus plus Infusion (N=80) n (%)		
Safety Population [a]	62	51	113	36	44	80	223	94
Final Study Disposition [b]								
Completed the Study	61 (98.4)	51 (100.0)	112 (99.1)	36 (100.0)	41 (93.2)	77 (96.3)	218 (97.8)	93 (98.9)
Discontinued from the Study	1 (1.6)	0	1 (0.9)	0	3 (6.8)	3 (3.8)	5 (2.2)	1 (1.1)
Reason for Discontinuation [b]								
Adverse Event	0	0	0	0	0	0	0	1 (1.1)
Lost to Follow-up	1 (1.6)	0	1 (0.9)	0	2 (4.5)	2 (2.5)	4 (1.8)	0
Withdrawal by Subject	0	0	0	0	1 (2.3)	1 (1.3)	1 (0.4)	0

[a] The Safety Population consisted of all subjects who were randomized and received any amount of andexanet or placebo.
[b] Percentages calculated from the number of subjects in the Safety Population.
[c] Study 11-501 (N=24 administered andexanet; N=8 placebo) was not pooled as discussed in Section 2.7.4.1.1.2.4.4.

Source: Summary of Clinical Safety page 34/173

Table 22: Study Disposition in the Confirmatory Study (14-505)

FXa Inhibitor n (%)[b]				Total receiving Andexxa
Patients Enrolled	Rivaroxaban	Apixaban	Enoxaparin	All Patients [a]
	24 (42.1)	27 (47.4)	6 (10.5)	57 (100)
All TEAEs	13	16	1	30 (52.6)
Deaths	3	5[d]	0	8 (14.0)
SAEs[c]	7	10	1	18 (316)
Discontinuation of study drug	0	0	0	0

a The Safety Population consisted of 57 subjects who were randomized and received Andexxa with evaluable data.
b Percentages calculated from the number of subjects in the Safety Population.
c Number of patients with an SAE.
d One death (unspecified accident for patient (b) (6)) did not have an SAE reported at the time of this report)

Source: Summary of Clinical Safety page 35/173

Reviewer Comment: Withdrawals from clinical trials are ubiquitous; the number of subjects who were withdrawn and the reasons for their withdrawal do not undermine the data or the conclusions drawn about the clinical trial.

8.4.4 Common Adverse Events

Overall, the incidence of treatment-emergent (TEAEs) was similar between the pooled Andexxa and pooled placebo analysis sets for any TEAE (53.2% vs. 59.3%) and TEAEs within the first hour of study drug administration (22.0% vs. 18.6%). TEAEs related to

study drug were higher in the Andexxa group (26.3% vs. 18.6%). The most common TEAE in the pooled Andexxa that was greater than placebo was infusion-related reaction (17.5% vs. 6.4%, respectively). The other most common AEs were either reported at similar rates between Andexxa and placebo (headache [7.6% vs. 7.4%, respectively]), or were more common in placebo subjects (dermatitis contact [2.2% vs. 7.4%], vessel puncture site pain [1.8% vs. 6.4%], respectively). The most common TEAEs related to study drug in the pooled Andexxa and pooled placebo analysis sets were infusion-related reaction (17.5% vs. 6.4%, respectively), and dizziness postural (1.3% vs. 3.2%, respectively).

The incidence of TEAEs in the combined Andexxa bolus only analysis set was 54%. The most common TEAEs were infusion-related reaction (18.6%), headache (11.5%), dermatitis contact (3.5%), and upper respiratory infection (4.4%).

The incidence of TEAEs in the combined Andexxa bolus plus infusion analysis set was 51.3%. The most common TEAEs were infusion-related reaction (16.3%), constipation (5%), and vessel puncture site hemorrhage (5%).

Table 23: Overview of Adverse Events in Healthy Volunteer Studies

Category Subjects With ≥1 AE	Andexxa Bolus			Andexxa Bolus + Infusion			Pooled Andexxa (n=223)	Pooled Placebo (n=94)
	400-420 mg (n=62)	600-800 mg (n=51)	Combined Bolus (N=113)	400-420 mg + infusion (n=36)	720-800 mg (n=44)	Combined Bolus + infusion (N=80)		
Any TEAEs n (%)	34 (54.8)	27 (52.9)	61 (54)	17 (47.2)	24 (54.5)	41 (51.3)	120 (53.8)	54 (57.4)
TEAEs related to study drug n (%)	16 (25.8)	11 (21.6)	27 (23.9)	11 (30.6)	10 (22.7)	21 (26.3)	58 (26.0)	17 (18.1)
TEAEs within the first hour of study drug exposure n (%)	17 (27.4)	10 (19.6)	27 (23.9)	6 (16.7)	8 (18.2)	14 (17.5)	48 (21.5)	17 (18.1)
TEAEs of special interest[a] n (%)	1 (1.6)	1 (2)	2 (1.8)	0	0	0	3 (1.3)	1 (1.1)
TEAEs leading to Premature discontinuation of study drug n (%)	0	0	0	1 (2.8)	0	1 (1.3)	1 (0.4)	0
SAE	0	0	0	0	0	0	0	0
Withdrawals from study due to AE	0	0	0				0	0
Deaths	0	0	0	0	0	0	0	0

Note: Study 11-501 (N=24 administered Andexxa; N=8 placebo) was not pooled
Source: Summary of Clinical Safety page 46/173

Table 24: Overview of Adverse Events in the Confirmatory Study (14-505)

Category Subjects With ≥1 AE	FXa Inhibitor			Andexxa (n=57) n (%)
	Rivaroxaban (n=24)	Apixaban (n=27)	Enoxaparin (n=6)	

	n (%)	n (%)	n (%)	
Any TEAEs n (%)	13 (54.1)	16 (59.3)	1 (16.7)	30 (52.6)
TEAEs related to study drug n (%)	1 (4.2)	1 (3.7)	0 (0)	2 (3.5)
TEAEs of special interest[a] n (%)	3 (12.5)	4 (14.8)	1 (16.7)	8 (14.0)
TEAEs leading to Premature discontinuation of study drug n (%)	0	0	0	0
Severe non-serious TEAEs n (%)	0	2 (7.4)	0	2 (3.5)
SAE n (%)	7 (29.2)	10 (37.0)	1 (16.7)	18 (32.0)
Fatal TEAEs[b] n (%)	3 (12.5)	4 (14.8)	0	7 (12.3)
Deaths n (%)	3 (12.5)	5 (18.5)	0	8 (14.0)

AE = adverse events; SAE = serious AEs; TEAE = treatment-emergent AE.
[a] AE of special interest were a thrombotic or embolic event of any severity; severe or serious infusion reaction.
[b] Eight Patients died in the safety population. One patient ((b) (6)) died from an unspecified accident on SD 8 but did not have a TEAE for the accident reported at the time of this report.
Source: Adapted from Summary of Clinical Safety page 47/173

Per Table 2.7.4-10 of the summary of Clinical Safety, 51 AEs were reported in 17 (53%) subjects enrolled in study 11-501. Of the 51 AEs, 44 were mild in severity and seven (2 infusion related reaction, 2 facial bones fracture, 1 headache, 1 nausea, and 1 pneumonia) were moderate in severity. None was severe, life-threatening, or fatal.

8.4.5 Clinical Test Results

Elevations of D-dimer, prothrombin fragment 1+2 were higher in the pooled Andexxa analysis set than the pooled placebo analysis set. These elevations were not associated with clinical evidence of thrombosis.

As noted previously, Andexxa completely inhibited TFPI activity approximately 3 hours after Andexxa bolus administration and returned to 25% of the pre-treatment level at 24 hours; data beyond the 24 hour time point is not available. TFPI activity was not investigated in phase 3 studies in the presence of FXa inhibitors; however, TFPI antigen was reduced to a similar degree in both phase 1 and 3 studies.

8.4.6 Systemic Adverse Events

Infusion-related Reactions
There were 102 events in 39 subjects in the Andexxa group and 14 events in 4 subjects in the placebo group. Most infusion-related reaction AEs were mild in severity. All infusion-related reactions were considered by the Investigator and this clinical reviewer as related to study drug and resolved. The infusion-related reaction symptoms that

occurred in ≥ 3 subjects were flushing (17 Andexxa), feeling hot (7 Andexxa, 1 placebo), cough (7 Andexxa), dysguesia (6 Andexxa, 1 placebo), dyspnea (6 Andexxa), chest discomfort (5 Andexxa, 1 placebo), palpitations, abdominal discomfort, urticarial, pruritus, and peripheral coldness, (3 Andexxa), and ocular hyperemia (2 Andexxa, 1 placebo).

No subjects in the Phase 3b/4 study (14-505) had an infusion reaction.

8.4.8 Adverse Events of Special Interest

Moderate or severe infusion reaction
Three subjects enrolled in study 12-502 had 8 moderate or severe infusion-related reactions that occurred within the first hour of infusion and were considered by the Investigator and this reviewer as related to study drug.

Thrombotic events (any severity)
Nine subjects in the confirmatory study had 16 AEs that were considered "potentially thrombotic in nature." The events occurred 2 to 30 days after dosing in subjects with medical histories of recent DVT alone ((b) (6) and (b) (6)), DVT/PE and atrial fibrillation ((b) (6) and (b) (6)), or atrial fibrillation alone ((b) (6)). None of the subjects were re-anticoagulated after treatment with Andexxa. Two of the thrombotic events (ischemic stroke on SD 2 in one subject and multiple DVTs on SD 3 in another) were considered related to Andexxa by this reviewer.

Table 25: Thromoembolic Events

Subject ID	Anticoag Dose/Freq	Indication	Bleed Site	Andexxa Dose	Event	SD	Investigator Causality	Reviewer Causality	Reanticoagulation (Y/N)
Apixaban									
(b) (6)	Apixaban 2.5 mg twice daily	Afib	M/S (intra-articular)	Low	acute MI	2	unrelated	**related**	No
	Apixaban	Afib	ICH	Low	cardiogenic shock/death	17	unrelated	unrelated	No
	Apixaban 5 mg twice daily	DVT	Visible	Low	DVT (multiple)	3	unrelated	**related**	No
					DVT (multiple)	11	unrelated	unrelated	
	Apixaban 2.5 mg twice daily	Afib	ICH	Low	DVT (L com fem)	28	unrelated	unrelated	No
	Apixaban 10 mg twice daily	Afib, VTE prev	Retroperitoneal	Low	Bilateral lower extremity DVTs	20	unrelated	unrelated	No
					cardiogenic shock	20	unrelated	unrelated	
					PE	19	unrelated	unrelated	
					Right atrial thrombus	20	unrelated	unrelated	

Rivaroxaban									
(b) (6)	Rivaroxaban 15 mg daily	Afib	ICH	High	ischemic stroke	2	related	related	No
	Rivaroxaban 20 mg daily	DVT	GI	High	PE	24	unrelated	unrelated	No
	Rivaroxaban 10 mg daily	Afib	ICH	Low	Embolic stroke	8	unrelated	unrelated	No
					DVT	14	unrelated	unrelated	
Enoxaparin									
(b) (6)	Enoxaparin 50 mg twice daily	VTE prev	Pericardial	High	infarct (L cerebral)	6	unrelated	unrelated	No
					infarct (post fossa)	6	unrelated	unrelated	
					infarct (right cerebral)	6	unrelated	unrelated	

Reviewer Comment: Thrombotic events are an expected AE as Andexxa has some procoagulant properties and because effectively reversing anticoagulation in patients who have an increased baseline risk for thrombosis increases the likelihood that such an event will occur. The lack of a control group makes it difficult to understand the clinical significance of these findings.

8.5.8 Immunogenicity (Safety)

The safety evaluation in nonclinical and clinical studies included the following measurements:

- antibodies directed against Andexxa itself;
- antibodies directed against the closely related parent protein, human FXa, and its precursor, FX; and
- a bioassay for potential interference by these antibodies with the function of Andexxa, FXa, or FX.

In each clinical study, samples from all subjects treated with either Andexxa or placebo were tested for the presence of antibodies against Andexxa, FX, and FXa.

The initial (b) (4) formulation had a very low rate of confirmed low titer non-neutralizing antibodies against Andexxa (2%) while the rate observed for the lyophilized formulation was higher (20%). Overall, 12.1% of healthy subjects had confirmed anti-Andexxa antibodies during the clinical development phase of Andexxa.

- Five subjects had titers of 1:40:
  - Subject (b) (6) (12-502 Module 4, 1280 mg) had a titer of 1:40 at SD 34-36 that increased to 1:2560 at SD 43-48.
  - Subject (b) (6) (12-502 Module 3, 210 mg) had a titer of 1:40 at SD 34-36 that increased to 1:640 at SD 43-48.
  - Subject (b) (6) (14-503 Part 1, 400 mg) had a titer of 1:40 at SD 43-48 only.
  - Subject (b) (6) (14-503 Part 2, 880 mg) had a predose titer of 1:10 and post-dose titers of 1:40 at all time points.

  - Subject (b) (6) (14-504 Part 1, 800 mg) had a titer of 1:40 at SD 34-36 that increased to 1:80 at SD 43-48.
- Four subjects had titers of 1:80:
  - Subject (b) (6) (12-502 Module 4, 600 mg) had a titer of 1:80 at SD 15-20, which decreased to 10 at SD 34-36.
  - Subject (b) (6) (14-503, 400 mg) had a titer of 1:80 at SD 43-48 only.
  - Subject (b) (6) (14-504 Part 1, 800 mg) had a titer of 1:80 at SD 34-36, which increased to 1:160 at SD 43-48.
  - Subject (b) (6) (14-504 Part 1, 800 mg) had a titer of 1:80 at SD 34-36 and 43-48.
- Subject (b) (6) (14-503 Part 1, 400 mg) had a titer of 1:160 at 15-20 which decreased to 1:80 at SD 43-48.
- Subject (b) (6) (14-504 Part 1, 800 mg) had a titer of 1:640 at 15-20 which decreased to 1:20 and 1:40 at SD 34-36 and 43-48, respectively.
- Subject (b) (6) (14-503 Part 2, 880 mg) had a predose titer of 1:10 and post-dose titers of 1:2560 at SD 15-20 which decreased to 1:320 and then 1:160.

Per the applicant, none of the antibodies were neutralizing "in that these samples did not prevent the ability of Andexxa to reverse anti-FXa activity resulting from anticoagulant addition."

Reviewer Comment: In this small database, the presence of non-neutralizing antibodies was not associated with clinically significant adverse events; however, the clinical implications of these antibodies for the general population are not known. As discussed previously in section 6.1.12.5, Portola has not developed assays to detect ADAs that may neutralize endogenous coagulation factors X and Xa. Their assertion that no neutralizing antibodies were detected is based on surrogate assessment (the presence of antibodies did not prevent Andexxa from reducing anti-FXa activity) and not by direct evaluation using a validated assay. The applicant claims that "from a product standpoint, the risk of immunogenicity of Andexxa is considered low as the endogenous protein (FXa) has no inherent immunomodulatory properties, and the recombinant protein (Andexxa) is of human origin and expressed in Chinese Hamster ovary cells with standard mammalian glycosylation." However, from a clinical standpoint, the development of a neutralizing antibody in a patient treated with Andexxa would significantly alter the risk-benefit profile of the drug; therefore, Portola should conduct studies that fully characterize the immunogenicity of Andexxa. Portola has committed to further evaluating immunogenicity in future studies. The immunogenicity incidence of 20% for the lyophilized product should be reported in the prescribing information and not the results of the liquid formulation (2%) or an overall incidence (12.1%) since these data are not relevant to the proposed marketed lyophilized product.

8.6 Safety Conclusions

The safety database is limited and the healthy volunteer data does not adequately inform of the safety of this product in the target population. The preliminary data from the confirmatory study does not identify any unanticipated safety risks but does provide some

evidence of a potential prothrombotic risk of Andexxa. As noted previously, the lack of a control group makes it difficult to interpret these data.

9. ADDITIONAL CLINICAL ISSUES

9.1 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.

9.1.1 Human Reproduction and Pregnancy Data

One subject in the phase 1 study 11-501 experienced an AE of spontaneous abortion following study drug administration. Serum pregnancy tests were negative at screening and Day -1. At the Day 28 follow-up visit the subject's pregnancy test was positive. The subject denied having unprotected intercourse and stated this was a false pregnancy. She refused to allow the release of her medical records. Approximately 2 months later she returned to the clinic and her pregnancy test was negative. The investigator considered this AE (chemical pregnancy which resulted in spontaneous abortion) possibly/probably related to study drug.

9.1.2 Use During Lactation

It is not known whether this drug is excreted in human milk, therefore. caution should be exercised when Andexxa is administered to a nursing woman.

9.1.3 Pediatric Use and PREA Considerations

This product 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) " on February 23, 2015; therefore pediatric studies were not required. The safety and efficacy of Andexxa in the pediatric population has not been studied.

9.1.5 Geriatric Use

In healthy volunteer studies of apixaban, rivaroxaban and enoxaparin, 20% (41/223) were ≥ 60 years old and 3% (6/205) were ≥70 years old. There were no clinically significant safety differences in safety or efficacy in this age group.

In the confirmatory study, 94% (33/35) of subjects were ≥ 60 years old and 80% (28/35) were ≥70 years old.

10. CONCLUSIONS

Significant safety concerns related to risk of thrombosis must be weighed against Andexxa's ability to provide therapeutic benefit to patients.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 26: Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the United States, direct FXa inhibitors such as Rivaroxaban (Xarelto), Apixaban (Eliquis), and Edoxaban (Savaysa) are approved for the prevention and treatment of thrombosis. • All are approved to reduce the risk of stroke in patients with atrial fibrillation (AF), which affects up to 2% of the population. The prevalence increases with age and with the anticipated rise in the average age of the population, it is likely that the rate of AF will rise considerably. There is a significant risk of stroke, heart failure and mortality associated with AF. • Serious or life-threatening bleeding is a labeled adverse reaction of FXa inhibitors. Serious and fatal bleeding was reported in phase 3 trials conducted to support licensure at an annualized rate of 2.1 to 3.5%. • The applicant estimates that >100,000 patients treated with FXa inhibitors will have a serious or life-threatening bleed annually in the US.	• Bleeding associated with anticoagulation is a serious condition. • Direct FXa inhibitors are being prescribed with increasing frequency, making this an important public health issue.
Unmet Medical Need	• Currently there are no approved therapies for the reversal of the anticoagulant effect of direct FXa inhibitors. • In patients experiencing a major bleeding event, current consensus-based guidelines recommend withdrawing the anticoagulant and providing "routine usual supportive care including fluid resuscitation, red blood cell transfusions, maintenance of renal function, identification of bleeding source, and surgical intervention as needed. • Consideration of the use of PCC, activated PCC or rFVIIa is also recommended; however, there is limited available data supporting the efficacy of these non-specific drugs for this indication.	• In patients experiencing life-threatening bleeding, there is an unmet medical need for effective reversal of anticoagulant effects.
Clinical Benefit	• Two clinical studies in healthy volunteers pre-treated with apixaban or rivaroxaban demonstrate that Andexxa decreased the pharmacodynamic anticoagulant effect of these drugs, as evidenced by reduced anti-FXa activity levels, for the duration of the infusion. • Data from an ongoing confirmatory study in patients being treated with FXa inhibitors and experiencing life-threatening bleeding may be indicative of clinical benefit in that, based on the sponsor's reported efficacy ratings, 24/31 (77%) received excellent or good efficacy ratings. FDA was unable to confirm the success adjudication in many cases due to uncertainty about the acuteness of the bleed and the lack of evidence to demonstrate cessation of bleeding for non-visible bleeding. For subjects with baseline	• The confirmatory study is ongoing. The preliminary data from this study is difficult to interpret due to the lack of a control group. The benefit in terms of reversal of anti-FXa activity may be limited to bleeding events that occur within the therapeutic range as reversal was subpar for subjects with baseline anti-FXa levels that were >2 SD of the mean levels observed in phase 3 healthy volunteer studies. Correlation between reduction of anti-FXa

	anti-FXa levels within therapeutic range, Andexxa effectively reversed anticoagulation by >80%. • Data were insufficient to support an indication for (b) (4) , enoxaparin and edoxaban.	activity and hemostatic efficacy may be difficult to establish. Furthermore, there were insufficient data submitted in the BLA to comment on the efficacy of this product in situations where prolonged reversal is mandated by standard of care (e.g., management of ICH).
Risk	• The most substantial risks of Andexxa are hypersensitivity reactions, inhibitor development, development of antibodies against CHO (b) (4) and thrombotic events. In healthy volunteer studies, most infusion-related reactions were mild in severity, and resolved without sequelae. No subject developed an inhibitor to FX or FXa. Healthy volunteer studies showed activation of the coagulation system following Andexxa infusion, but not thrombotic events were observed. Nine subjects in the confirmatory study had 16 thrombotic events, including two that were considered related by this clinical reviewer. It is unclear if this rate is comparable to what would be observed in a control group. • Of the 57 patients in the safety population of the confirmatory study, 37 SAEs were reported in 18 subjects, including 1 that was considered related to the product.	• The safety database in the target population is relatively small. Furthermore, investigation of antibodies against CHO (b) (4) is inadequate. • Interpretability of the data is limited by the lack of a control arm. • The risk of thrombosis is high in the target population due to the fact that these patients have a higher baseline risk of thrombosis which is unmasked with reversal of anticoagulation. The use of a drug with potential procoagulant properties may increase that risk under these circumstances.
Risk Management	• Andexxa is a reversal agent for FXa inhibitors.	• If approved, the applicant is required to complete the confirmatory study to convert the approval from an accelerated approval. The confirmatory study protocol requires revision, including provision to use the results of the planned usual care cohort study as a comparator for the hemostatic co-primary endpoint. • The package insert and the current pharmacovigilance plan, including postmarketing studies to evaluate additional dosing regimens and immunogencity, would be adequate to manage the risks.

11.2 Risk-Benefit Summary and Assessment

Serious or life-threatening bleeding is a labeled adverse reaction of FXa inhibitors. The applicant estimates that >100,000 patients treated with FXa inhibitors will have a serious or life-threatening bleed annually in the US. Currently there are no approved therapies for the reversal of the anticoagulant effect of direct FXa inhibitors. In patients experiencing a major bleeding event, current consensus-based guidelines recommend withdrawing the anticoagulant and providing routine usual supportive care including fluid resuscitation, red blood cell transfusions, maintenance of renal function, identification of bleeding source, and surgical intervention as needed. Consideration of the use of PCC, activated PCC or rFVIIa is also recommended; however, there is limited available data supporting the efficacy of these non-specific drugs for this indication. The availability of a reversal agent would increase treatment options by providing a more targeted therapy.

Risks

The safety concerns for this product are hypersensitivity reactions, thromboembolic events, and the development of FX inhibitors and antibodies against CHO (b) (4) . The ability to clearly define these risks in the target population, and therefore for this product, is limited by the size of the safety database, and lack of sufficient investigations of immunogenicity (*e.g.*, antibodies against CHO (b) (4) and FX inhibitors). Although none of the 57 subjects treated in the ongoing confirmatory study (14-505) were positive for FX binding antibodies, it is unclear if any subject developed inhibitors to FX or antibodies against CHO (b) (4) because testing for these antibodies was not done. Most infusion-related reactions were mild and resolved without incident. Of the 16 reported thrombotic events in 9 subjects, 2 were considered related to the product by this reviewer. Of the 37 SAEs that were reported in 18 subjects, one (ischemic stroke) was considered related. The potential for these risks should be discussed in a boxed warning and the Warnings and Precautions sections of the Package Insert, if the product is eventually approved.

Benefits

The benefit of this product derives from its ability to reverse anticoagulation. The efficacy of Andexxa for a limited indication of reversal of direct FXa inhibitors apixaban and rivaroxaban in life-threatening or uncontrolled bleeding has been demonstrated by data from healthy volunteer studies demonstrating that Andexxa can effectively reverse anticoagulation for the duration of the infusion as evidenced by reduction in anti-FXa activity. These conclusions were supported in part by preliminary data from the confirmatory study, which demonstrated that for bleeds with anticoagulant levels in the therapeutic range, Andexxa can effectively reverse anticoagulation.

For apixaban, efficacy was demonstrated in 122 subjects enrolled in clinical trials of Andexxa, including 46 (38%) that were studied with the proposed licensed dose. At all doses studied (90 to 900 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. In general, anti-FXa activity returned to placebo levels within 2 hours after completion of administration

and for subjects dosed within the therapeutic range, Andexxa resulted in >90% reduction in anti-FXa activity.

For rivaroxaban, efficacy was demonstrated in 95 subjects enrolled in in clinical trials of Andexxa, including 44 that were studied with the proposed licensed dose. At all doses studied (210 to 1760 mg), Andexxa reduced anti-FXa activity within 2 to 5 minutes and the depth of reversal was sustained during the continuous infusion. In general, anti-FXa activity returned to placebo levels within 2 hours after completion of administration and for subjects dosed within the therapeutic range, Andexxa resulted in >90% reduction in anti-FXa activity. However, as noted above, 20% of subjects dosed within the therapeutic range had less-than-expected reduction in anti-FXa activity levels which was not seen with Apixaban and suggests that the higher dose may be more effective as a reversal agent.

Results from preliminary data from the ongoing confirmatory study in patients being treated with FXa inhibitors and experiencing life-threatening bleeding may be consistent with clinical benefit in that based on EAC adjudication 24/31 (77%) received excellent or good efficacy ratings. However, in the absence of control data the clinical significance of these findings is questionable.

In summary, the benefits of this product are due to its efficacy in reversing anticoagulation as evidenced by reduction in anti-FXa activity, the preliminary hemostatic efficacy results in the target population and consideration of the unmet medical need. The thrombotic risks from reversal of anticoagulation can be significant and clinicians will have to weigh these risks against the potential benefits before prescribing this drug.

11.3 Discussion of Regulatory Options

The regulatory options considered included:

1. No approval due to the limited safety database, inadequate evaluation for inhibitor development and concerns for inadequate assessment of the drug's procoagulant properties (TFPI contribution).
2. Approval for a broad indication of all FXa inhibitors based on a class effect, contingent on having a FDA-approved design for the confirmatory and Usual Care cohort studies.
3. Approval for a narrow indication based on the limited duration of effect, contingent on having a FDA-approved design for the confirmatory and Usual Care cohort studies.

Concerns for the procoagulant properties of Andexxa, the inadequate assessment of the TFPI contribution to its mechanism of action, the inadequate immunogenicity assessments in the clinical development program, and the limitations of the safety database in the target population prompted discussion about possibly not approving this product. In addition, the lack of an apparent correlation between anti-FXa and hemostatic efficacy and the return of anti-FXa activity to near baseline levels following completion of the infusion raised questions about the adequacy of the proposed surrogate to predict

clinical benefit. These concerns were discussed in several meetings, including during the midcycle meeting held on March 24, 2016 (with Dr. Epstein), and subsequent meetings with CBER management on March 30, 2016 (with Christopher Joneckis), and April 27, 2016/May 9, 2016 (Dr. Peter Marks), and were also communicated to Portola in the Midcycle Communication which prompted them to escalate their dispute to the Immediate Office of the Center Director. The safety and efficacy issues were re-evaluated throughout the review cycle as additional data/information were made available by Portola through responses to information requests and the submission of additional safety day in the 180-day Safety Update. Consideration was given to the unmet medical need that this product addresses, the seemingly low incidence of related thrombotic events (without a control group it is difficult to comment on the significance of these findings), the lack of antibody development noted in clinical trials of Andexxa, and Portola's commitment to evaluate these issues in future studies. A decision not to reject the surrogate based on the preliminary data from the confirmatory study was made by CBER and OBRR management; the regulatory action would be based on data from the completed phase 3 healthy volunteer studies and data from the confirmatory study were to be used to inform on the safety of the product and to help improve the study design of the confirmatory study.

Based on the submitted data, reversal of anti-FXa activity during the duration of the Andexxa infusion was demonstrated in healthy volunteer subjects who were anticoagulated with apixaban and rivaroxaban. Because this application is being reviewed under accelerated approval using anti-FXa activity, duration of effect is based on reversal of anti-FXa activity only, and not on or with consideration of normalization of thrombin generation. As Andexxa's duration of effect was not sustained after completion of the infusion, the review team decided to limit the approvable indication to a short-term reversal. The exact terminology that will be used to convey to the treating physicians that the duration of effect is limited and should be considered when treating conditions where prolonged reversal is suggested/required, such as in ICH, will be determined during labeling negotiations. As a result of differences in PK/PD and *in-vivo*/*ex vivo* (e.g., ED50, etc.) parameters across anticoagulants, a broad indication for all FXa inhibitors (i.e. direct and indirect inhibitors) was not approvable. Furthermore, data to support the use of Andexxa for edoxaban and enoxaparin were too limited to consider approval.

An approval for a limited indication of short-term reversal of direct FXa inhibitors apixaban and rivaroxaban in life-threatening or uncontrolled bleeding was considered, contingent on the following:

1. The final design of the confirmatory and usual care cohort studies are agreed upon by FDA prior to approval.
2. A commitment from Portola to evaluating immunogenicity, thrombin generation and TFPI, and additional dosing regimens (additional doses, longer infusions). If commitments are not made, a complete response is recommended.

Approval for edoxaban, enoxaparin (b) (4) procedures was not recommended as limited to no data were submitted in the BLA to support these indications. In order to support an indication of reversal for edoxaban and enoxaparin, FDA advised Portola that

additional data was needed to evaluate safety and efficacy for these indications. For enoxaparin, a justification for the use of anti-FXa as a surrogate based on mechanism of action and PD, and for the proposed benchmark criterion proposed for the analysis of hemostatic efficacy is required if Portola plans to license Andexxa under accelerated approval for this indication.

11.4 Recommendations on Regulatory Actions

At the time of completion of this memo, a Complete Response is recommended because FDA and Portola have not reached agreement on an adequate design of the confirmatory and Usual Care Cohort studies. Furthermore, additional information regarding Andexxa's procoagulant properties is needed to adequately assess the safety of this product in the target population.

11.5 Labeling Review and Recommendations

The proposed proprietary name, Andexxa, was reviewed by the Advertising and Promotional Labeling Branch (APLB) from a promotional and comprehension perspective and determined to be acceptable. Labeling claims for reversal of anticoagulation effect of edoxaban and enoxaparin were not supported by the submitted data; this was communicated to Portola in the filing notification letter. The package insert, carton and container labels submitted to BL STN 125586/0 were not negotiated during this review cycle.

If approved, the package insert should clearly identify the limitations of the safety and efficacy databases, highlight the risks for thrombotic events in a boxed warning and clearly state that this product was not evaluated for repeat or longer than 2 hour infusions.

11.6 Recommendations on Postmarketing Actions

The confirmatory study will be considered a post-marketing requirement study. Additional clinical studies to evaluate immunogenicity and additional dosing regimens may be warranted, depending on the final design of the confirmatory study.

Appendix I. Consult Responses
Appendix II. Complete schedule of assessments
Appendix III. Rating Scale for Endpoint Adjudication