<table>
<tr><td>Application Type</td><td>Original Application-Response to Complete Response Letter</td></tr>
<tr><td>STN</td><td>125586/0</td></tr>
<tr><td>CBER Received Date</td><td>August 4, 2017</td></tr>
<tr><td>PDUFA Goal Date</td><td>May 4, 2018 (Revised following a Major Amendment Decision)</td></tr>
<tr><td>Division / Office</td><td>DCEPT /OTAT</td></tr>
<tr><td>Priority Review</td><td>Not applicable</td></tr>
<tr><td>Reviewer Name(s)</td><td>Bindu George, MD</td></tr>
<tr><td>Review Completion Date / Stamped Date</td><td>04/23/2018</td></tr>
<tr><td>Supervisory Concurrence</td><td>Tejashri Purohit-Sheth, MD</td></tr>
<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>Coagulation Factor Concentrate</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>
<table>
<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>ANDEXXA is a recombinant modified human Factor Xa (FXa) protein indicated for patients treated with FXa inhibitors, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.</td></tr>
<tr><td>Orphan Designated (Yes/No)</td><td>Yes</td></tr>
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APPROVED
By Bindu George at 10:18 pm, Apr 22,

APPROVED
By Tejashri Purohit-Sheth, M.D. at 6:59 am, Apr 23, 2018

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GLOSSARY

ADAE	analysis dataset adverse events
ADD	action due date
AE	adverse events
AFib	atrial fibrillation
AESI	adverse events of special interest
BLA	biologics licensing application
CAD	coronary artery disease
CI	confidence interval
CMC	chemistry manufacturing controls
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRL	complete response letter
CSR	clinical study report
CT	computed tomography
DVT	deep venous thrombosis
GCS	glasgow coma scale
GI	gastrointestinal
GIB	gastrointestinal bleed
EAC	endpoint adjudication committee
FDA	food and drug administration
HIT	heparin-induced thrombocytopenia
HVS	healthy volunteer studies
ICD	implantable cardioverter defibrillator

ICH	intracranial hemorrhage
IND	investigational new drug
INR	international normalized ratio
IR	information request
MA	major amendment
MedDRA	medical dictionary for regulatory activities
PCC	prothrombin complex concentrates
PD	pharmacodynamic
PE	pulmonary embolism
RCT	randomized controlled trial
SAP	statistical analysis plan
SGE	special government employees
TEAE	treatment-emergent adverse events
TEE	thromboembolic events
TFPI	tissue factor pathway inhibitor
UCC	usual care cohort
VT	ventricular tachycardia
VTE	venous thrombo-embolism

I. Executive Summary

ANDEXXA (ANDEXXA) is a recombinant modified human coagulation factor Xa (fXa) protein, inactivated. This is Portola's resubmission of a marketing application to a Complete Response Letter issued on August 17, 2016. The original BLA was submitted on December 18, 2015. The applicant seeks marketing approval under the Accelerated Approval pathway for reversal of anticoagulation in patients treated with rivaroxaban and apixaban for the reversal of life-threatening or uncontrolled bleeding.

In the original BLA submission, the applicant reported on two completed Phase 3 studies (14-503 and 14-504) for reversal of anticoagulation following treatment with apixaban or rivaroxaban in healthy volunteers as the primary studies intended to support a marketing approval. The applicant also submitted data from one Phase 2 study (Study 12-502) in healthy volunteers to support marketing approval for the indication of reversal of anticoagulation related to edoxaban and enoxaparin treatment. In addition to the healthy volunteer studies, data from 35 subjects from the ongoing Phase 3b/4 study ANNEXA-4 (Study 14-505) of ANDEXXA for the treatment of subjects who experienced life-threatening bleeding following anticoagulation with rivaroxaban, apixaban or enoxaparin were also included. The efficacy endpoint to support a marketing claim was based on the surrogate endpoint of change in anti-fXa activity in the healthy volunteer studies (HVS). ANNEXA 4 study was designed and is being conducted to serve as the confirmatory study to evaluate the efficacy of ANDEXXA in the target (bleeding) population.

The adequacy of anti-fXa activity as a surrogate was of concern to the review team at the time of filing and during the review of the original submission such that an advisory committee meeting was planned for June 20 and 21, 2016. Please refer to Summary of Pre-submission regulatory activity, Sections 5.4.1. 7.1.11 and 11.3 of Dr. Faulcon's review memo. However, plans for an advisory committee meeting were cancelled for reasons unclear to the review team. The clinical recommendations of efficacy were, therefore, based on the effect of ANDEXXA on reversal of anticoagulation based on anti-fXa activity, the preliminary but questionable clinical significance of the hemostatic response observed in the ANNEXA 4 study and the unmet medical need. Please refer to discussion of benefit-risk in Page 17 of Dr. Fauclon's review memo.

A Complete Response Letter (CRL) was issued on August 17, 2016, following review of the original submission, mainly related to Chemistry, Manufacturing, and Controls (CMC) issues. The clinical issues identified in the CRL related to the lack of an agreement on the design of a confirmatory study and insufficient data to support an efficacy claim for reversal of bleeding related to edoxaban and enoxaparin.

In this resubmission received on August 4, 2017, the applicant provided data from 185 safety-evaluable subjects from the ongoing study in bleeding subjects (ANNEXA 4). Subjects who received one dose of ANDEXXA were considered evaluable for safety. Hemostatic efficacy based on the change in anti-fXa activity at baseline and at 12 hours following treatment with ANDEXXA from 98 efficacy-evaluable subjects who experienced bleeding following treatment with apixaban and rivaroxaban were also

included. The review of this resubmission focused on the safety issues from the updated safety data from the ANNEXA 4 study and on the evaluation of correlation between the surrogate endpoint and hemostatic efficacy. The major review issues relate to:

1) The lack of correlation between change from baseline anti-fXa activity (surrogate endpoint) and hemostatic response in the 185 subjects from the ANNEXA 4 study.
2) A 17.8% risk of thrombosis, ischemic events or risk of sudden death observed in the ANNEXA 4 study that represent a three-fold increase in the risk for these events as compared to literature-based historical data.
3) A detailed review for hemostatic efficacy in the 106 evaluable subjects was not performed as the study is ongoing. Conclusions regarding efficacy are difficult to interpret in this single-arm study in the absence of a reliable control group.
4) The above findings raise substantial concern regarding the robustness of the surrogate endpoint and approval under the accelerated approval pathway and re-emphasize the need for a controlled study designed to increase the interpretability of the data and reduce bias, such as a randomized controlled study.
5) The potential for increased thromboembolic and ischemic risks coupled with the uncertainties identified in this submission (of the response to the CRL) regarding a) the adequacy of change from baseline to post-treatment anti-fXa activity as a reasonably likely surrogate form the basis for an unfavorable benefit-risk assessment and b) the uncertainties as to the clinical significance of the preliminary efficacy results of hemostatic efficacy (per the applicant's assessment) of the ANNEXA 4 study and weighed in the context of efficacy results in the published literature with the use of usual care treatments such as PCC that has since become available (available after the original submission).
6) A Usual Care Cohort (UCC) control study was planned and discussed briefly during the review of the original submission. The usual care cohort is intended to serve as a control to the ANNEXA 4 study. The treatment in the UCC study would consist of usual care as determined by the investigator. The review of the UCC study identified numerous deficiencies which were communicated to the applicant on February 16, 2018.
7) Unresolved concerns that were identified during the review of Studies 14-504 and 14-503 in the original submission and the additional data from the ANNEXA 4 study provided in this submission relate to the short duration of reversal of anti-fXa activity.

The clinical reviewer does not recommend marketing approval of ANDEXXA. For details of the clinical and regulatory basis and considerations for this recommendation, please refer to Section VI of this review. The clinical reviewer further recommends that the applicant consider a randomized controlled study to support the safety and efficacy of ANDEXXA. The reviewer recommends that such a study(ies) be completed prior to consideration for a marketing approval under the traditional approval pathway using hemostatic response as the primary endpoint.

II. Clinical and Regulatory Background

This section summarizes

A. Two key clinical issues identified during the review of the original submission that were not included in the CRL letter.
B. Issues that were identified in the CRL letter.

The summary of the key clinical review issues and CRL issues is to serve as a background to the review issues discussed in Section IV. For example, The original submission identified insufficient data to correlate change from baseline anti-fXa activity due to the limited sample size of 35 subjects. Additional data from 98 efficacy-evaluable subjects were provided in this submission. Therefore, in this submission, the review team performed an analysis of correlation between the surrogate endpoint and hemostatic efficacy in these 98 subjects

For details of the regulatory activity prior to and during the submission of the Original Submission, please refer to Dr. Lisa Faulcon's clinical review memo stamped on August 12, 2016.

A. Key clinical review issues identified in the original submission

Issue #1: Insufficient Data in the Original Submission to correlate anti-fXa activity to hemostasis.

- Insufficient data to allow meaningful conclusions to be drawn regarding correlation between decrease in anti-fXa activity and hemostatic efficacy. As excerpted from Dr. Faulcon's review: "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 ANDEXXA administration questions the adequacy of anti-FXa activity as a surrogate marker likely to predict clinical outcomes." In addition, Dr. Faulcon's review memo notes "These preliminary data show that the depth of reversal is not as robust in patients presenting with supra-therapeutic anti-FXa levels."

- Please also refer to the regulatory background section in Dr. Faulcon's clinical review memo, specifically the discussions related to the November 13, 2015 Type A meeting with Portola. Of concern to the review team was the limited number of subjects in the planned efficacy and safety dataset from ANNEXA 4 that would be available at the time of the original submission in December 2015. At the time of the original submission, the review team expressed the opinion that the data from ANNEXA 4 would be insufficient to evaluate for correlation between the PD effects (surrogate endpoint) of ANDEXXA and hemostatic efficacy. To address the review team's concern CBER and OBRR management advised the review team to procced with filing the BLA and review the submitted clinical data, with the caveat that if the clinical data from ANNEXA 4

were found to be insufficient to demonstrate correlation of PD parameters to clinical benefit (hemostatic efficacy), then the review team was to consider making a regulatory recommendation based solely on the biologic plausibility of ANDEXXA's effect on hemostasis.

Reviewer 's comments: Since additional clinical data were available in this resubmission as compared to the original submission, additional analyses were performed to evaluate the comparability in the magnitude of the change in anti-fXa level noted in the HVS (healthy volunteer Phase 3 studies) and the ANNEXA 4 study. The correlation between the surrogate endpoint and hemostatic responses were analyzed within the ANNEXA 4 study. The results of the analyses and conclusions have been presented in Section IV.C of this review.

Issue #2: Study design of the confirmatory study

Please refer to Dr. Faulcon's review memo of BLA 125586 (original submission) for details of the regulatory background related to the design of the confirmatory study prior to the original submission.

- The design of the confirmatory study remained an unresolved issue at the time of filing of the original submission. Discussions regarding a randomized controlled study design began prior to the original submission (please refer to the Advice letter dated August 3, 2015).
- The applicant communicated their disagreement with this advice through an informal teleconference with CBER management. Subsequently, a final decision made by the FDA and conveyed to the applicant on September 4, 2015 was that "a RCT was offered as an option to be considered" and reaffirmed that the Agency was not insisting on this design approach. The Agency agreed that a historical control was acceptable, but noted that the applicant's proposal to consider the efficacy results from the Kcentra study to serve as a benchmark for efficacy of ANDEXXA would not be acceptable.
- During the review of the original submission, two Type A meetings were held on February 24, 2016 and April 20, 2016, to discuss the design of a study. An agreement was reached in principle in support of a Usual Care Cohort study as a control cohort for the ANNEXA 4 study with the caveat that the design of such a study was yet to be finalized.
- During the review of the original submission two special government employee (SGEs) (hematology and neurology) consultations were obtained to opine as to the design, assessment methods, endpoints of the ANNEXA 4 study and the duration of reversal of anti-fXa activity noted in the healthy volunteer studies. The SGE consultative review/communications attached to Dr. Faulcon's review memo of the original submission document the opinions that RCT studies are feasible in the target population.

- The applicant submitted a revised UCC study protocol under IND 15089 to address the clinical issues in the CRL. Based on the agreements reached on April 20, 2016, the applicant submitted a synopsis of the planned UCC and a revised ANNEXA 4 study protocols.
- A study protocol was submitted on June 10, 2016, the FDA provided numerous comments related to the applicant's proposed revisions. A summary of the key issues is provided below:
    - Include a propensity score stratification instead of propensity score matching for primary efficacy analysis
    - Consider a dynamic/adaptive enrollment to ensure that the distribution of critical covariates are similar between ANNEXA 4 and UCC studies
    - FDA disagreed with the applicant's plans for premature study termination
    - Provide revised sample size calculations based on magnitude of benefit proposed
    - Blinding of study adjudicators for the assessment of safety and efficacy
    - Discrepancies in the time points for efficacy assessments between ANNEXA 4 and UCC studies

The timing of the efficacy assessments in the UCC study mirrored those in the ANNEXA 4 study. Therefore, the FDA had advised the applicant to finalize revisions to the ANNEXA 4 study prior to finalizing the UCC study. Based on the communication from the applicant on June 10th, additional revisions to the ANNEXA 4 study were planned. However, since no further revisions to the ANNEXA 4 study were provided, the review of the UCC study submitted on June 30, 2017 was postponed until the ANNEXA 4 study was revised. However, the applicant did not submit the agreed upon revised ANNEXA 4 protocol.

B. Clinical issues identified in the CRL

A complete response letter (CRL) was issued on August 17, 2016.

- A substantial number of issues identified in the CRL letter relate to CMC deficiencies. Please refer to CMC review memo for details.
- The clinical issues listed in the letter were related to:
    1. Reaching an agreement with the Agency regarding the design of the confirmatory trial prior to approval of the BLA
        - FDA noted that the preliminary data available in the original BLA submission from the first 35 subjects in the ANNEXA-4 study were difficult to interpret for both efficacy and safety. The difficulty in interpretation of the clinical data were due to enrollment of subjects who did not meet the eligibility criteria, questions related to the adjudication process and concerns that the transient change from baseline anti-fXa activity may be insufficient to treat intracerebral hemorrhage (ICH) caused by a factor Xa inhibitor.

- FDA noted that an agreement had not been reached regarding the primary efficacy endpoint and the statistical analysis plan to evaluate the success criteria for the ANNEXA 4 study based on the comparison of hemostatic outcomes between the ANNEXA 4 study and the control cohort (usual care cohort study-UCC study).

2. Insufficient data to support an indication for reversal of anti-fXa activity due to the
   - Limited magnitude of reversal of anti-fXa activity following exposure to edoxaban as noted in the healthy volunteer studies.
   - The limitations of use of anti-fXa activity alone as a surrogate measure of reversal of anticoagulation related to enoxaparin. Enoxaparin has a dual pathway that is related to its effect on factors Xa and IIa.

3. An additional statistical comment requesting that the applicant update the analysis for Study 14-504 using a pre-specified imputation method to include all 14 subjects instead of the 13 subjects proposed by the Applicant.

In the CRL letter, FDA offered to further discuss the clinical issues related to the CRL in a separate meeting. A type A meeting was held on October 27, 2016 to discuss clinical issues (in addition to CMC issues) stated in the CRL letter. Key items discussed during this meeting were:

- That the FDA had no objection to the applicant's plan to exclude hemostatic efficacy claims related to reversal of enoxaparin- and edoxaban-caused bleeding from the resubmission.
- An agreement on the design of the ANNEXA-4 and UCC study would be sufficient for marketing approval and enrollment of subjects to the UCC study would be important evidence of the applicant's commitment to completing the confirmatory study.
- Review of the safety database may identify additional issues that may need to be addressed prior to marketing approval.

Regulatory interactions during review of the resubmission

Please see Appendix B for the summary of regulatory interactions during the review of this resubmission.

Reviewer's comments: In summary, in this response to the CRL, there were numerous deficiencies and inadequate responses from the Applicant to our information requests with regard to 1) missing data related to safety of subjects in ANNEXA-4, 2) quality issues with data tables 3) discrepancies in the safety data. The missing data and the data discrepancies noted in the applicant's multiple responses to FDA's requests for information, posed a challenge in completing the clinical review

in a timely manner to meet the action due date for this review cycle. A major amendment was required to review the substantial amount of clinical information related to safety provided in Amendment 96 and submitted on December 18, 2017, approximately six weeks before the due date.

III. Clinical Review Strategy

The clinical review focused on:

1. Review of the applicant's response to clinical issues conveyed in the CRL
2. Evaluation of safety data based on the updated data from the ANNEXA 4 study
3. Analysis of the correlation between anti-fXa activity and hemostatic response based on the updated results from the ANNEXA 4 study.

    - Comparison of the change in anti-fXa activity noted in the healthy volunteer studies (HVS) (Studies 14-503 and Studies 14-504) and the ANNEXA 4 study. This comparison was performed to assess whether the rate of change in anti-fXa observed in the HVS was comparable to the ANNEXA 4 study.
    - Correlation of the change from baseline anti-fXa activity and the hemostatic responses observed in the ANNEXA 4 study. This analysis was performed to assess whether the change from baseline anti-fXa activity was reasonably likely to predict hemostatic efficacy of ANDEXXA.

The clinical review did not focus on:

- The preliminary efficacy data in the ANNEXA 4 study were not evaluated in support of a regulatory recommendation given the limitations in interpreting the efficacy data in the absence of control and therefore is pending the completion of the UCC study.
- An integrated summary of safety analysis was not performed because the population and the risks associated with thromboembolic events and all-cause mortality were substantially different between the subjects in the ANNEXA 4 study and the healthy volunteer studies.
- An updated pharmacovigilance plan with the confirmatory studies were not included in this submission. The applicant was notified via a teleconference on February 15, 2018 that a randomized controlled trial (RCT) would be necessary to evaluate the efficacy of ANDEXXA in the bleeding population and that the data from the ANNEXA 4 and UCC study would be supportive in the interpretation of efficacy. An RCT study protocol was submitted on March 16, 2018 and feedback was provided to the applicant on March 23. A revised RCT study was submitted on March 30, 2018 and is under review. On February 16, 2018, the applicant received the clinical reviewer's comments regarding major deficiencies identified upon review of the UCC study submitted on June 30, 2017 to IND 15089.

IV. Clinical Review

This section summarizes the review as follows:

A. Review of CRL response to clinical comments
   1. Absence of control data
   2. Labeling indication to include edoxaban and enoxaparin reversal

B. Review of updated data from ANNEXA 4 study
   1. Evaluation of safety data based on the updated data from the ANNEXA 4 study
      a. Disposition of the safety population
      b. Safety population – demographics and baseline characteristics
      c. Adverse Events
         1. Adverse Events of Special Interest (AESI)
            a. Thromboembolic events
            b. All-cause 45-day mortality
            c. Infusion reactions
         2. Heparin-Induced Thrombocytopenia (HIT)
         3. Adverse Events by Organ Systems
         4. Additional safety analyses
            a. Dose-Thromboembolic Event (TEE) relationship
            b. AESI and anticoagulant use
            c. Immunogenicity

   2. Surrogate endpoint (change from baseline anti-fXa activity) assessment

      a. Disposition of the efficacy population
      b. Comparison of the surrogate endpoints in the ANNEXA 4 study and healthy volunteer study
      c. Analysis of correlation between surrogate endpoint and hemostatic response (clinical benefit endpoint)
      d. Analyses of durability of the change in anti-fXa activity
      e. Analyses of correlation between time from last exposure to anti-fXa and pre-treatment (baseline) anti-fXa level

A. Review of CRL responses to clinical comments

1. Absence of control data

UCC study

At the time of the original submission of this BLA, a synopsis of the UCC study was reviewed. The UCC study is intended to provide prospective, concurrent control data with usual care treatment to compare the efficacy and safety outcomes from the single-arm ANNEXA 4 study of

ANDEXXA. A complete study protocol and statistical analysis plan (SAP) was not provided during the review of the original submission. The Applicant submitted a study protocol and SAP to the IND (15089) on June 30, 2017. The UCC study was not included as a confirmatory study under the BLA. The UCC study was reviewed and major deficiencies related to the protocol and SAP were communicated to the applicant via an advice letter under the IND on February 16, 2018. A revised protocol to reach an agreement on the design of this confirmatory study is pending.

Randomized controlled Trial (RCT)

Additional data from the ANNEXA 4 study became available for review as part of the CRL response. FDA's clinical review of this data raised two major concerns:

a) the inability to demonstrate a correlation between the surrogate endpoint (i.e., change from baseline anti-fXa activity) and hemostatic response (clinical benefit endpoint) (Section IV.B.2.) and

b) concerns that rate of thromboembolic rates were 3-4-fold higher than anticipated for the population at risk. (Section IV.B.1)

On February 15, 2018, the FDA communicated the need for an RCT study to further understand the findings from the ANNEXA 4 study. Based on the review and the deficiencies identified in the UCC design, the FDA considered the RCT study be the optimal to better assess the two major concerns identified above.

Status of the RCT study: As of the time of the finalization of the review, additional revisions are being made to the RCT design based on the review of this study. The proposed RCT is intended to compare the hemostatic outcomes in patients with intracranial hemorrhage (ICH) between ANDEXXA and usual care treatment in approximately 440 subjects. The feasibility of conducting such a study post-approval of ANDEXXA under accelerated approval is yet to be determined.

In summary: A proposal for the RCT study was introduced during the review of this submission based on the review findings from the updated date from the ANNEXA 4 study in the response to the CRL. Agreements are pending on the design of two confirmatory studies; a RCT and the UCC studies and therefore continues to be a review issue at the time of finalization of this memo. An addendum to this memo to record the status of the agreements regarding the RCT and UCC study will be provided prior to ADD.

2. Labeling indication for reversal of edoxaban and enoxaparin

In the CRL letter, FDA communicated that there was insufficient data to support a marketing claim for reversal of edoxaban and enoxaparin. The applicant has revised the indication statement in the label to exclude the claim.

From the clinical reviewer's perspective, the proposal to not seek a marketing claim for reversal of edoxaban and enoxaparin with ANDEXXA adequately addresses the issue.

B. Review of data from the ANNEXA 4 study

1. Evaluation of updated safety data from ANNEXA 4 study

a) Disposition

Please refer to Appendix A of this review for details of the study design and statistical considerations.

The results of the safety analysis of 185 safety-evaluable subjects in the ANNEXA 4 study are discussed in Section IV.B.1. For detailed information of safety assessments related to healthy volunteer studies, please refer to Dr. Faulcon's review memo. In the healthy volunteer studies (HVS), the most common treatment emergent adverse event (TEAE) was infusion reaction. Elevated D-dimers and prothrombin fragment F1+F2 and complete inhibition of TFPI; biomarkers of a pro-coagulant state, were observed in the HVS. A pooled analysis of the subjects in the HVS and ANNEXA 4 is not planned due to the differences in the safety profile of these subjects.

Disposition of Subjects

Screened subjects: 203

Total number of screen failures: 18

Table 1: Disposition

Eligibility criteria not met	11
Withdrew consent	2
Investigator decision	4
Other	1

- Enrolled/Treated subjects: 185
- Safety-evaluable subjects (Subjects who received any dose of ANDEXXA for reversal of apixaban, rivaroxaban, edoxaban or enoxaparin related bleeding): 185 subjects.

The table below depicts the demographic information for the 185 subjects.

b) Safety population – demographics and baseline characteristics\

Table 2: ANNEXA 4 Demographic characteristics (for the safety-evaluable population)

Type of Baseline Characteristics (n=185)	Sub type of baseline characteristics	Number of subjects (%)
Race	White	154 (83%)
	African American	26 (14%)
	Asian	1 (0.5%)
	Native American	1 (0.5%)
	Other	1 (0.5%)
Age	<65 years	24 (29%)
	65- ≤75 years	109 (59%)
	>75 years	52 (28%)
Sex	Female	89 (48%)
	Male	96 (52%)
Type of bleeding	ICH	106 (57.3%)
	Gastrointestinal (GI)	58 (31.4%)
	Other	21 (11.3%)
Type of anti-fXa	Apixaban	98 (52.9%)
	Rivaroxaban	72 (38.9%)
	Enoxaparin	14 (7.6%)
	Edoxaban	1 (0.05)
Reason for fXa inhibitor treatment	Atrial fibrillation	130 (70.2%)
	Atrial fibrillation and venous thromboembolism (VTE) prevention or treatment*	24 (13%)
	VTE treatment	17 (9%)
	VTE prevention	12 (6.4%)
	Other	2 (1.1%)

Source: FDA clinical reviewer

* Subjects had both VTE and atrial fibrillation as the underlying reasons for anti-coagulation.

Reviewer comments: The enrollment based on distribution by age and gender is acceptable and representative of the population at risk. The number of screen failures is acceptable for the size of the safety-evaluable set.

c) Adverse Events

(1) Adverse Events of Special Interest (AESI)

The protocol-specified AESI were thromboembolic events and infusion reactions. For the purposes of FDA analyses, all-cause 45-day mortality

was also included in the AESI analysis. For additional details please refer to Appendix A.

(a) Thromboembolic events (TEE)

Of the 185 safety-evaluable subjects, 109 subjects experienced an adverse event. The protocol- specified definition of adverse events of special interest (AESI) includes only acute myocardial infarction, deep venous thrombosis, pulmonary embolism, ischemic or embolic or unknown reasons for a stroke. FDA's assessment of thromboembolic events included cases of acute respiratory failure, congestive heart failure, cardiogenic shock, ventricular tachycardia, cardiac thrombus, cardiac arrest, or iliac artery occlusion. In instances where alternate explanations for the event were observed in the review of the narratives and data sets, the event was excluded from a TEE. For example, respiratory failure improving with antibiotics or treatment of Chronic Obstructive Pulmonary Disease (COPD) were excluded from the FDA-AESI analysis. The selection of adverse events towards the FDA-AESI analysis included acute respiratory failure, congestive heart failure, cardiogenic shock, congestive heart failure, ventricular tachycardia, cardiac arrest, cardiac thrombus and iliac artery occlusions as these events in the absence of alternate causes may represent manifestations of ischemic events. Based on the protocol-specified AESI definition, 27 (14.5%) subjects experienced 30 such events. Based on the reviewer's/FDA definition of TEE AESI, 33 subjects (17.8%) of the safety-evaluable subjects experienced 43 AESI. The difference in the applicant's analysis and the FDA analysis is based on protocol-defined AESI, where relevant, the reviewer has provided analysis based on the protocol-specified and FDA-assessed AESI. Of the 33 subjects who experienced FDA-AESI, 18 (54%) were enrolled for ICH, 12 (36%) were enrolled for GI bleeding and 3 (0.9%) for other causes of bleeding. Of the 27 subjects who experienced protocol-specified AESI, 14 (52%) were enrolled for ICH and 10 (37%) were enrolled for GI bleeding and 3 (11%) were enrolled for other bleeds.

Table 3: AESI

AESI (total number of subjects - 185)	**Number of events***	**Female (n-15)**	**Male (n=18)**
Acute myocardial infarction*	5	2	3
Acute respiratory failure	2	2	0
Cardiac arrest	1	0	1
Cardiac thrombus	1	1	0

AESI (total number of subjects - 185)	Number of events*	Female (n-15)	Male (n=18)
Cardiogenic shock	3	2	1
Congestive heart failure	2	0	2
Deep venous thrombosis*	11	5	6
Embolic Stroke*	1	1	0
Iliac artery occlusion	1	0	1
Ischemic stroke*	8	4	4
Pulmonary embolism*	5	2	3
Sudden cardiac death	1	0	1
Sudden death	1	0	1
Ventricular tachycardia	1	1	0
Total number of AESI events	43	20	23

* 43 FDA defined AESI occurred in 33 subjects. 30 protocol-specified AESI occurred in 27 subjects.
Source: FDA clinical reviewer

Table 4: FDA-AESI by bleed type

Bleed type	ICH	GI (n=58)	Other (n=21)
FDA-AESI	18 (16.9%)	14 (24%)	3 (14.2%)
Protocol specified AESI	14 (13.2%)	10 (17.2%)	3 (14.2%)

Table 3 above, was derived following review of the applicant's response dated 02/26/18, to the FDA IR request from 01/29/18. In this response, the applicant provided narratives for subjects who were noted to have congestive heart failure, respiratory failure, ventricular tachycardia or elevated troponin. Table13 in APPENDIX F provides a brief description of the events and the FDA clinical reviewer's basis for adjudicating these events.

Reviewer comments: There were 43 thrombotic, ischemic or sudden death events that occurred in 33 subjects. Thus 17.8% of subjects treated with ANDEXXA experienced such events. The incidence of the protocol-specified AESI and the FDA-assessed AESI are approximately three-fold higher (4-5%) than the risks observed historically from a population at risk for thrombotic events for whom anticoagulation was reversed (please refer to Appendix C). For example, in the interim analysis of safety in the confirmatory study to support accelerated approval of idarucizumab in 2015, the thromboembolic events in bleeding population (n=66) was 4.5% and in the surgical cohort (n=57) was 3.5%. The rate of TEE in subjects with GI bleeding was higher than with ICH. Therefore, it is unlikely that enrollment of higher risk (of TEE) subjects,

i.e., ICH bleeding is an explanation for the higher than anticipated rate of TEE. The incidences of these events were similar for male and female subjects (1.3 events per female subject and 1.2 events per male subject). Thus, gender-based concerns with risk of TEE were not observed.

(b) All-cause 45-day mortality

The protocol-specified analysis for deaths was based on an observation period of 30 days from ANDEXXA infusion. However, for the 30-day assessment visit, the protocol allowed follow-up of up to 45 days. Therefore, the FDA analysis is based on 45-day all-cause mortality in some cases where subjects died after the 30-day assessment, which and differs from the applicant's analysis.

Table 5: All-cause mortality

Safety population (n=185)	Deaths in the Safety Population (n=25)	Deaths as per Protocol specified AESI (n=6)	Deaths as per the FDA-AESI population (n=10)
ICH n=106 (57.3%)	15 (60%)	3 (50%)	7 (70%)
GI n=58 (31.4%)	6 (24%)	0	1 (10%)
Other n=21 (11.4%)	4 (16%)	3 (50%)	2 (20%)

Source: FDA clinical reviewer

Reviewer's comments

The all-cause mortality rate was 13.5% in this study and comparable to the all-cause mortality noted historically in patients who were treated for bleeding with reversal of anticoagulation and had pre-existing risk of thrombosis. In addition, considering the small sample sizes, within the ICH sub-group of subjects the rates of all-cause mortality were similar in the safety, protocol-specified AESI (50%) and FDA-AESI (70%) population. Therefore, the observed all-cause mortality rate (50-70%) in the ICH sub-group is comparable to the proportion of ICH subjects who were enrolled into the study (57.3%). Thus, the underlying type of bleeding, particularly ICH, is unlikely to have been the major contributor to the all-cause mortality. This observation may be explained by the favorable inclusion criteria in the protocol. For example, subjects with the GCS <7 or intracerebral bleeding volume >60 cc were excluded from the trial. Both GCS (a predictor of 30-day mortality) and bleed volume (a predictor of hematoma expansion and mortality) are prognostic factors with regard to ICH. Thus, in interpreting the all-cause mortality with ANDEXXA and

comparing it to historical data, for example with idarucizumab or the study by Majeed (2017), the comparability of the population in terms of morbidity and mortality risks need to be considered.

The mortality reports pertain to the observation period of up to 45 days (range: 1-51 days). Of the 25 deaths reported, the median time to death from ANDEXXA infusion was 16 days (range: 1-44 days). Eight of these deaths occurred within 10 days after the infusion.

(c) Infusion reactions

No infusion reactions reported in the ANNEXA 4 study.

(2) Heparin-Induced Thrombocytopenia (HIT)

The applicant noted that two subjects (Subject (b) (6) and (b) (6)) experienced HIT. Of the two subjects, one (Subject (b) (6)) developed thrombocytopenia, a second episode of DVT (note: first episode of DVT was not related to HIT and therefore included in the FDA-AESI analysis) and platelet factor 4 antibodies (PF-4) and serotonin release assay that was weekly positive, confirming the diagnosis of HIT which was temporally related more to heparin than to ANDEXXA. Information regarding the temporal association of the thrombocytopenia and PF-4 antibodies in relation to heparin exposure was not available in the datasets and in the response to the IR submitted on 02/26/18. This information regarding the temporal association to the heparin was made available during the subsequent labelling negotiations. Subject ((b) (6)) was experiencing a septic event when the diagnosis of HIT. In this subject, HIT could not be confirmed by SRA. In summary one subject developed HIT following heparin exposure.

Reviewer's comment: The rate of HIT is within the expected rate for patients admitted to critical care units. Therefore, inclusion of information regarding HIT in Section 6 (Adverse Events section) is adequate.

(3) Adverse events by organ systems

Overall there were 368 events of all grades and 93 Grade 3-4 toxicity and 36 grade 5 events. The majority of the Grade 3-4 events were pulmonary or infectious in nature, occurred in less than 5% of subjects, and were typical of adverse events often observed in elderly and ICH patients. These adverse events do not raise substantial concerns, with the exception of subjects who experienced FDA-assessed AESI, as mentioned above.

Table 6: AEs by Age

Subjects	Age	Grade 3	Grade 4	Grade 5	Total

N=80	> 75 years	49 (19%)	26 (10%)	18 (6%)	259
N=30	65-75 years	8 (9%)	4 (4%)	5 (6%)	84
N=12	<65 years	0 (0%)	5 (20%)	1 (4%)	25

Source FDA clinical reviewer

Reviewer's comment: Overall the incidence of Grade 3 toxicity is higher in subjects > 75 years of age; however, the incidence of Grade 4 toxicity is higher in <65 years of age and Grade 5 toxicity is comparable across all age groups. Given the small sample size in subjects who are < 65 years of age, conclusions about severity of toxicity and advanced age is challenging. Overall subjects who were > 75 years of age were at higher risk of Grade 3 or greater toxicity. This may be consistent with age-related susceptibility to adverse events. Given the discrepancy in the rate of Grade 5 toxicity (lower in the subjects > 75%) years of age, the interpretation of increased toxicities in subjects >75 years of age is challenging. For these reasons, the reviewer does not recommend that the label state that there are increased risks to subjects > 75 years of age.

(4) FDA additional analyses

(a) Dose-Thromboembolic Event (TEE) relationship

The protocol specified a single administration of 400 mg or 800 mg of ANDEXXA; the dosage was determined by the type and timing of the last dose of anticoagulant. The safety analysis examined the relationship between dose and FDA-assessed AESI and protocol-specified AESI.

Table 7: Dose-FDA-AESI relationship

Population	**# of subjects receiving 800 mg**	**# of subjects receiving 400 mg**	**Total # of subjects**
Safety-evaluable	20	165	185
% of safety-evaluable subjects by dose cohort who developed FDA defined AESI	3 (15%)	29 (17.6%)	32
% of safety-evaluable subjects by dose cohort who developed protocol defined AESI	3 (15%)	20 (12.1%)	23

Source: FDA clinical reviewer

Reviewer's comments: The substantially smaller proportion of subjects who received the higher dose of ANDEXXA is noted. Therefore, the results are interpreted in the context of the small sample size of subjects who received high-dose ANDEXXA. Thus, the TE rates are proportional to the number of subjects who received high-dose and low-dose ANDEXXA. The reviewer concludes that a correlation between dose and TEE was not observed.

(b) Anticoagulant use and TEE

An analysis was performed to evaluate the impact of the timing of anticoagulation (i.e., no anticoagulation; anticoagulation initiated prior to TEE; anticoagulation initiated after the TEE) on the rate of TEE.

Table 8: TEE rate and anticoagulant use

Population	**Bleed Type**	**No anticoagulation (n= 81)**	**Anticoagulated (n=104)**		
			Total	**Prior to event**	**After the event**
Experienced FDA-AESI events or death (n=45)	All	17 (20.9%)	29 (27.8%)	11 (10.5%)	18 (17.3%)
	ICH	11 (13.6%)	18 (17%)	9 (8.6%)	9 (8.6%)
	GI	4 (4.9%)	6 (5.8%)	1 (0.9%)	5 (4.8%)
	Other	2 (2.5%)	5 (4.8%)	1 (0.9%)	4 (3.8%)
Did not experience FDA-AESI events or death (n=139)	All	64 (79%)	75 (72.1%)		
	ICH	43 (53%)	35*		
	GI	19 (23.5%)	29*		
	Other	2 (2.5%)	16*		

Reviewer's comment: The thromboembolic rate in patients who did not receive anticoagulation was twice the rate in subjects who were anticoagulated before the event. This difference in thromboembolic rates was noted most in subjects who experienced GI bleeding. These results should be interpreted with caution given the small sample size of subjects who received anticoagulation before the event. For subject IDs of subjects who were anticoagulated and experienced an event or death, please refer to Appendix E.

(c) Immunogenicity

Subjects were evaluated for anti-ANDEXXA antibodies and antibodies to human factor Xa for up to 45 days post-ANDEXXA.

Antibody type	**Screening (n=162)**	**Day 30 (n=83)**	**Day 45 (n=26)**
Anti-ANDEXXA	Not confirmed (n=3)	Not confirmed (n=4)	Not confirmed (n=4)
	Not detected (n=159)	Not detected (n=76)	Not detected (n=19)
		Confirmed (n=3) (1:10, 1:80, 1:160)	Confirmed (n=3) (1:10, 1:20, 1:20)
Anti-fXa	n=162	n=87	n=26
	Not confirmed 1 of 3*(n=51)	Not confirmed n=19	Not confirmed n=1
	Not confirmed 2 of 3 (n=12)	Not detected N=68	Not confirmed n=25
	Not confirmed 3 of 3 (n=0)		
	Not detected 3 of 3 (n=99)		
	Not detected 2 of 3 (n=51)		
	Not detected 1 of 3 (n=12)		

*When the screening test (test for detection) was positive in 1 of 3 samples, the sample that was positive on screening (detected) was then tested using a confirmatory test. For example, 51 subjects were noted to have positive samples for anti-fXa antibody based on 1 of 3 samples. In this case, confirmatory testing was performed in those samples from these 51 subjects (one sample per subject) that were positive by the screening assay. The same paradigm was followed for testing if screening tests were positive in 3 of 3 or 2 of 3 samples.

Anti-ANDEXXA antibody results were available for 164 subjects. Of these subjects, anti-ANDEXXA antibody test results were available for 109 subjects at follow-up either at the 30-day or 45-day assessment timepoints. Of these 109 subjects considered evaluable for anti-ANDEXXA antibodies, 6 (5.5%) of subjects developed anti-ANDEXXA antibodies. All 3 subjects with confirmed anti-ANDEXXA antibodies had decreasing titers at Day 45. The time to clearance of these antibodies is unknown given the absence of data beyond Day 45.

Reviewer's comments: The reviewer's conclusions are drawn from the limited sample size. The results do not raise substantial concerns with regard to development of neutralizing antibodies to fXa. The clinical relevance of anti-ANDEXXA antibodies in the treatment is unclear and may need to be evaluated in the context of long-term presence of these antibodies and its blocking effect on ANDEXXA activity should a patient experience another bleeding event that requires treatment with ANDEXXA. The applicant has proposed a surgical study to evaluate the effect of re-dosing and further studies may be necessary to evaluate the effect of the antibodies in treatment of a bleeding event that is distal to the previous bleeding event. The proposed indication is for one dose of ANDEXXA and therefore the reviewer does not recommend additional precautions in the label. The reviewer recommends that information regarding the presence of anti-ANDEXXA should be included in the label.

2. Surrogate Endpoint

a) Disposition of the Efficacy Population

Since the total number of subjects (n=106) in the efficacy-evaluable population who experienced bleeding on apixaban and rivaroxaban is different from the number of subjects (n=185) in the safety population, a summary of the disposition of the efficacy-evaluable population is provided prior to the discussion of the results of the surrogate endpoint.

Of the 185 efficacy-evaluable subjects, 108 subjects in the ANNEXA 4 study had complete data to perform the analyses to assess the relationship between reduction in anti-fXa activity and hemostatic efficacy.
The disposition from an analysis perspective is described below:

- Efficacy-evaluable subjects (subjects who had a baseline anti-fXa level > 75 ng/mL related to apixaban, rivaroxaban, edoxaban or enoxaparin related bleeding): 108 subjects
- Reasons for excluding 77 safety-evaluable subjects from the efficacy-evaluable population
    - Baseline anti-fXa level < 75ng/mL (pre-specified in the study protocol): 36 subjects (19% of the safety-evaluable population)
    - Missing baseline anti-fXa level (considered administrative reasons for ineligibility per protocol definition): 36 (19.5% of the safety-evaluable population)
    - EAC determined as not eligible based on the severity of bleeding: 3 (0.01% of the safety-evaluable population)
    - Adjudication data not available: 2 subjects (0.01% of the safety-evaluable population)

Of the 108 efficacy-evaluable subjects,

- 61 subjects received apixaban, 45 received rivaroxaban and 2 received enoxaparin.

54, 39, 13 subjects had ICH, GIB and other bleeding events, respectively, related to apixaban or rivaroxaban.

b) Comparison of the surrogate endpoint in the ANNEXA 4 study and healthy volunteer study

The change from baseline anti-fXa levels in the ANNEXA 4 and HVS studies were compared to evaluate whether the treatment effects on the surrogate endpoint were comparable. The tables for change from baseline anti-fXa levels in the HVS study as confirmed by Dr. Faulcon and ANNEXA 4 study are provided. For the details of the HVS studies, please refer to Dr. Faulcon's memo, a summary of the studies have been provided in Appendix H.

Table 9: ANNEXA 4 Summary of change from baseline anti-fXa levels

FXa	**N**	**Nadir value Median (95%CI)**	**Absolute change median (95%CI)**	**% change in median (95% CI)**
All	98*	11.1 (9.5, 13.5)	-146.6 (-161.4, -125.9)	-92.3% (-93.6%, -90.3%)
Apixaban	56	10.7 (8.5, 12.4)	-142.3 (-157.1, -117.7)	-92.3% (-94.1%, -91.5%)
Rivaroxaban	40	13.5 (9.1, 25.3)	-165.8 (-195.8, -137.8)	-90.6% (-93.8%, -86.7%)

*The total number of subjects do not total up to 106 evaluable subjects as noted in the discussion related to disposition of the efficacy-evaluable subjects.

Reviewer's comments: The mean percent change from baseline to nadir in anti-fXa activity level for apixaban and rivaroxaban in the ANNEXA 4 study are consistent with the mean percent change noted for apixaban and rivaroxaban in Studies 14-503 and 14-504. Comparable magnitude of reduction in anti-fXa activity levels (apixaban and rivaroxaban) were noted in the healthy volunteer studies and subjects in the ANNEXA 4 (ANNEXA 4 study). Of the 106 subjects, a few of the subjects did not have nadir values available for analysis. The analysis performed by the applicant provided for similar results, thus the conclusions from these analyses are not impacted by the differences in 8 subjects.

c) Analysis of correlation between surrogate endpoint and hemostatic response

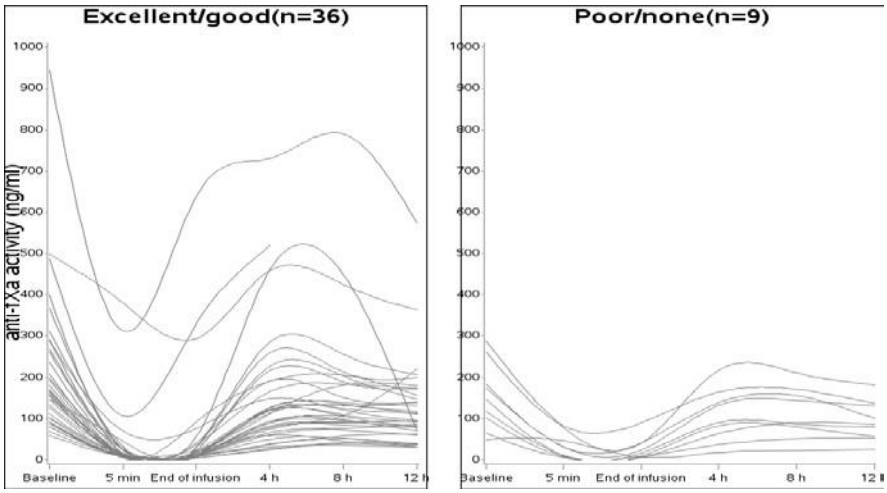
In the original BLA submission, the data from 35 subjects in the ANNEXA 4 study was considered insufficient to determine the correlation between the change in the surrogate endpoint and hemostatic efficacy. The deficiencies with the adjudication of efficacy in itself precluded preliminary assessment

of such a correlation. The recommendation by the clinical review team to consider a marketing approval was based solely on biological plausibility as directed by CBER management.

With the availability of additional data from the ANNEXA 4 study in the response to the CRL, the statistical reviewer analyzed the relationship between change from baseline to nadir anti-fXa level to excellent/good hemostatic response and to poor/none hemostatic response.

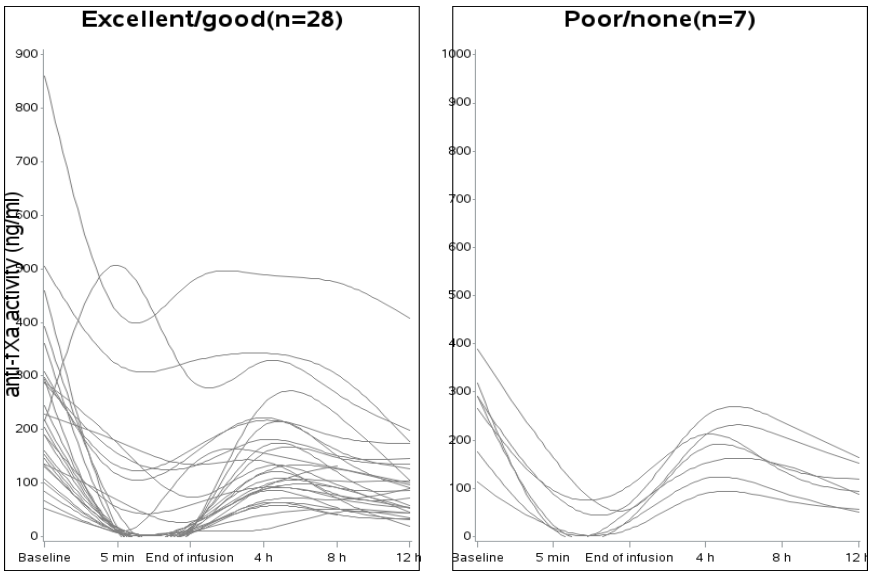
As discussed in Section IV.B.2.b) the results of the change from baseline to nadir levels of anti-fXa in the HVS and ANNEXA 4 study are comparable. Therefore, it is reasonable to further evaluate the correlation between the surrogate endpoint and hemostatic outcomes (clinical benefit). The result of the change in anti-fXa and hemostatic outcomes are discussed below.

Figure 1:Time course of anti-fXa activity by hemostatic outcome for apixaban



Source: FDA statistical reviewer

Figure 2: Time course of anti-fXa activity by hemostatic outcome for rivaroxaban



Source: FDA statistical reviewer

Table 10: Change in surrogate endpoint and pre-treatment anti-fXa activity level

Baseline anti-fXa activity (ng/mL)	Number of subjects	Mean percent change (decline) from Baseline (Range) in anti-fXa activity	Absolute change (decline) from Baseline in ng/mL (Range) in anti-fXa activity	Hemostatic response / Efficacy outcome
75-149	27	90.71 (67.44-96.36)	100.07 (65.90-140.40)	Excellent or Good
	4	92.45 (87.22-95.07)	110.83 (94.30-138.80)	Poor or None
150-299	30	83.54 (-33* – 97.92)	176.05 (72.00*-288.90)	Excellent or Good
	8	81.75 (64.58-92.39)	196.19 (152.50-269.50)	Poor or None
≥300	13	67.72 (0.60-98.10)	351.35 (186.90-652.80)	Excellent to Good
	2	91.66 (86.66-96.66)	323.5 (309.50-337.20)	Poor or None

*Indicates an increase from baseline anti-fXa activity.

The above results were derived from datasets with a cut-off date of April 20, 2017

Reviewer's comment: The primary intent of this review is not to evaluate the hemostatic outcomes in the ANNEXA 4 study. Therefore, the analyses presented above in evaluating the correlation between the surrogate endpoint and hemostatic efficacy is based on the analyses of the adjudicated hemostatic outcomes as submitted in the response to CRL.

The figures above suggest that reduction in anti-fXa levels from baseline were similar in subjects with "excellent/good" and "poor/none" hemostatic efficacy outcomes. Furthermore, the table above, suggests that hemostatic outcomes did not correlate with hemostatic outcomes across different baseline anti-fXa levels. In some instances, hemostatic excellent or good hemostatic outcomes were achieved in subjects who had an increase in levels from baseline anti-fXa activity levels or in subjects with levels as high as 652.80 ng/mL.

In making the conclusion below, the reviewer considered the a) the inability of the data from 108 efficacy-evaluable subjects from ANNEXA 4 to demonstrate a correlation that is distinct between the anti-fXa activity and excellent/good vs poor/none hemostatic response, b) the observation that hemostatic responses were noted despite post-ANDEXXA post-nadir levels that were substantially greater than threshold levels in the study (>75ng) for assessing efficacy, and c) historical efficacy and safety data from the results from the single-arm study to provide context to the interpretation of the efficacy using available therapies. For example, the observed hemostatic efficacy with PCC was 69% successful hemostatic rate in the overall group (all bleed types), 72% in ICH and 60% in the GI subgroups in a study by Majeed et al (Appendix C).

These findings raise the concern that despite the larger sample size available as compared to the original submission, correlation to support the surrogate endpoint of anti-fXa reduction as reasonably likely to predict for hemostatic response is yet to be demonstrated. The overall hemostatic efficacy (clinical benefit) observed in the ANNEXA 4 study is not interpretable given the absence of control data and the absence of correlation between anti-fXa (PD) and hemostatic efficacy. The reviewer concludes that the PD parameters are adequately reversed for a transient duration in the intended population. However, the absence of correlation between the PD parameters and hemostatic efficacy in the 185 evaluable subjects and the abbreviated durability of change in anti-fXa activity raise substantial doubts as to the preliminary evidence of effectiveness of the product and the likelihood that the surrogate endpoint is reasonably likely to predict for hemostatic response.

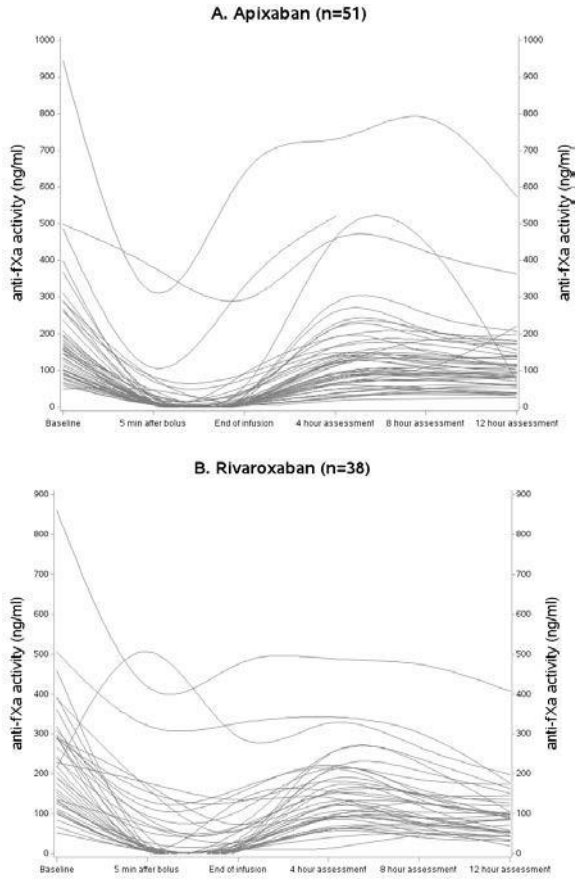
Absent the correlation between the surrogate endpoint and the efficacy outcomes, the regulatory basis for approval is unclear. Therefore, the reviewer does not recommend marketing approval of ANDEXXA for reversal of apixaban and rivaroxaban-related bleeding. If a marketing approval is planned, a clear explanation of the basis for a regulatory decision in the context of these findings would be necessary.

d) Analyses of the durability of change in anti-fXa activity

Another major review issue identified in Dr. Faulcon's review related to the durability of the change from baseline anti-fXa activity (reversal of anti-fXa activity) in the HVS studies.

As such, this reviewer focused on the durability of change from baseline anti-fXa activity in the ANNEXA 4 study, and the following figure, adapted from the statistical reviewer's memo, depicts the time series change from baseline of anti-fXa levels following ANDEXXA treatment.

Figure 3: Time series change from baseline anti-fXa following ANDEXXA treatment for apixaban and rivaroxaban (From FDA statistical reviewer's analysis)



Reviewer's comments: The change from baseline anti-fXa activity is transient, with a rise in anti-fXa activity noted almost immediately following the end of ANDEXXA infusion. The transient nature of the reversal of anti-fXa activity was noted in the HVS studies, 14-503 and 14-504. The results of this study continue to raise concerns about the transient nature of the reversal of anti-fXa activity and confirms that the results are consistent between the HVS and the intended population (bleeding subjects). For purposes of discussion in this memo, the term "rebound" refers to the rise in anti-fXa activity that follows at the end of infusion, that approaches levels that are consistent with the levels noted in the placebo arm at comparable time points. As noted in Dr. Faulcon's review, in Study 14-504 (rivaroxban), these levels exceed the levels noted in the placebo arm. As noted in Dr. Faulcon's review of Study 14-504, the rebound effect following the high dose infusion suggests re-bound anti-fXa levels were higher than the levels observed in the

placebo group at the corresponding time points in each of the arms. In the absence of control data in the ANNEXA 4 study, this concern regarding the higher rebound in the ANDEXXA arm vs. the placebo arm noted in the HVS cannot be verified in the intended population.

e) Analysis of correlation between time from last exposure to anti-fXa and pre-treatment (baseline) anti-fXa level

The treatment effect and study success is to be analyzed in subjects who have target anti-fXa level of >75ng/mL. In the absence of a companion diagnostic for anti-factor Xa, it is important to analyze whether the criteria (time from last anticoagulant dose) for selecting high vs low dose and patient selection in the post-marketing setting were predictive of the threshold level of anti-fXa that is to be used for efficacy analyses. This analysis is presented below:

Table 11: Relationship between time from last dose of anti-fXa and pre-treatment baseline anti-fXa levels

Type of fXa inhibitor	Number of subjects with available baseline anti-fXa levels	Mean Baseline anti-fXa levels (ng/mL)	Median Baseline anti-fXa level (ng/mL)	Number of subjects with baseline anti-fXa levels > 75ng/mL (% of subjects based on available baseline levels)
All	**142**			**110 (77.5%)**
≤ 7 hours (time from last dose)				
Apixaban	5	260.3	207.3	4 (80%)
Rivaroxaban	3	137.8	131	2 (66.7%)
>7 -18 hours (time from last dose)				
Apixaban	74	154.5	128	57 (77%)
Rivaroxaban	56	205.7	168.7	43 (76%)
Unknown (time from last dose)				
Apixaban	2	144.5	144.5	2 (100%)
Rivaroxaban	2	130	130	2 (100%)

Source: FDA clinical reviewer

Reviewer's comments: Of the 185 subjects who received one dose of ANDEXXA, 142 subjects had a test to determine the baseline anti-fXa level. Ninety-one percent (n=130) of subjects who had such baseline anti-fXa levels, had baseline levels > 75ng/mL. Differences in the baseline anti-Xa levels were minimal between the two groups of subjects based on time from last dose of anticoagulant (≤7 hours vs >7 to 18 hr). The reviewer's conclusions discussed below should be interpreted with caution as 43 (23.2%) subjects did not have baseline anti-fXa levels and the possibility of bias from missing data remains a concern. Based on the analysis above, the majority of subjects entered the study with baseline anti-fXa levels that were above the threshold required for treatment consideration with ANDEXXA. Therefore, despite the absence of a plan for co-

development, the predictive ability of the clinical parameter of time from last dose of the anticoagulant is reasonable (77.5%) to select subjects who are above the threshold level of 75ng/mL. In theory, for every 200 patients who receive the product based on these clinical parameters, 46 are likely to have received the product even though the anti-fXa levels were less than 75ng/mL. Of these 46 subjects, 17% may be at risk for TEE based on the FDA-assessed AESI TEE rate (described in Section IV.B.1 of this review). If the anticipated risk of TEE from underlying causes is 4-5% (as has been observed in published literature) the net risk from ANDEXXA is approximately 13% or 5 patients for every 200 treated. The risk of thrombosis in patients who would otherwise have received ANDEXXA should be made in the context of a complete assessment of risks and efficacy. Therefore, at this time there is insufficient data to recommend a requirement for a companion diagnostic.

3. ANNEXA 4 Summary of Review Conclusions

- The rate of FDA-assessed AESI suspicious for thromboembolic and ischemic risk of 17.8% is higher than the rate observed in studies in similar populations in the published literature. (Appendix C)
- The rate (17.8%) of FDA-assessed AESI suspicious for thromboembolic and ischemic risk and/or death in this study with prophylactic anticoagulation appears to be higher than the expected rates observed in the published literature.
- The all-cause mortality rate of 13.5% is within, or perhaps lower, than the expected rate, based on the observed rates for a similar population in the published literature. This data should be interpreted in the context of the enrollment criteria that stipulated that subjects at higher risk of mortality and morbidity (GCS <7, intracerebral bleeding > 60cc) were to be excluded from the study.
- In subjects who were enrolled for treatment of ICH-related bleeding, the all-cause mortality rate was consistent with the proportion of subjects with ICH who were enrolled into the study. Thus, ICH subjects were unlikely to be at greater risk of death as a result of ANDEXXA treatment.
- The rate of investigator-assessed HIT of 0.5% is within the expected rate for critically ill patients.
- A relationship between high vs. low dose of ANDEXXA and FDA-assessed AESI suspicious for thromboembolic and ischemic risk was not observed.
- The most common AEs were pulmonary and infectious adverse events at frequencies less than 5%. Therefore, non-AESI events are not a major safety concern.
- The change from baseline to anti-fXa levels are reproducible in the HVS and target population in the ANNEXA 4 study.
- Reduction in anti-fXa levels from baseline was noted to be similar in subjects with “excellent/good” and “poor/none” hemostatic efficacy outcomes. This raises the concern that despite the sample size of 185

subjects, correlation to support the surrogate endpoint of anti-fXa reduction as reasonably likely to predict for hemostatic response has yet to be demonstrated.

- An in-depth efficacy analysis of the ongoing ANNEXA 4 (has not been performed. However, based on the applicant's analyses, the hemostatic efficacy as rated by the independent EAC for patients in the complete efficacy population (n=74) demonstrated that 57 patients (81.4%; 95% CI 0.66-0.86)) achieved either Excellent or Good hemostasis following ANDEXXA treatment. In a single-arm prospective study by Majeed et al of 84 patients with life-threatening bleeding (ICH, GI and other) with 4-factor PCC as treatment (standard of control), the hemostatic efficacy rate was 69.1% (95% CI; 0.41-0.71) for all patients, with successful outcomes in 72.8% of patients with ICH: 72.8% and 60% of subjects with GI bleeding. Although not intended as a comparator for regulatory decisions, the preliminary results of the ANNEXA 4 study are not suggestive of a substantial benefit over available therapies with concerns that the lower bounds of the 95% CI may be within the upper bounds of the usual care treatment as observed in the PCC study by Majeed et al.
- Given the potential that the treatment effect of ANDEXXA may at best be marginal, while the thromboembolic risks appear to be increased substantially, an RCT may be necessary to demonstrate effectiveness of the product.
- Therefore, an RCT to evaluate the benefit of ANDEXXA may be necessary and should be completed prior to marketing approval of ANDEXXA.

C. Benefit-Risk Assessment

The benefits of ANDEXXA largely rest on the biologic plausibility of reversal of the PD parameter.

- The major review issues are
  - The data from 108 efficacy-evaluable subjects do not demonstrate a correlation to support that the reduction in anti-fXa level can be correlated with hemostatic outcomes. Furthermore, the observation that subjects with anti-fXa levels well above the 75 ng/mL threshold (supra-therapeutic thresholds) who experienced less than optimal reversal of anti-fXa also experienced good/excellent hemostatic efficacy. The two findings taken together raise concern that uncertainties around the threshold levels that predict for hemostasis remain, that the correlation between change from baseline anti-fXa activity and excellent/good vs. poor/none hemostatic response has yet to be demonstrated and brings into question the validity of anti-fXa as predictive for hemostatic efficacy.
  - The transient nature of the durability of the reduction in anti-fXa levels raise concerns about the effectiveness of the product given that most life-threatening bleeding events such as ICH

may require longer duration of reversal. It is unclear in the absence of control where the observed efficacy in ICH subjects represent an improvement over no treatment. Such an assessment would require a randomized controlled study or concurrently controlled study. However, the short duration of reversal may be of benefit in these subjects when the risk of re-bleeding/hematoma expansion is highest between 3 and 6 hours after the initial ICH bleeding event.

- The preliminary assessment of efficacy of ANDEXXA based on the applicant's analysis does not represent a substantial benefit over available therapies.
- The thromboembolic and ischemic risks associated with ANDEXXA, raise the concern that thrombotic risks may be higher than in the at-risk population subject to reversal of anticoagulation. The results should be interpreted with caution since the historical control data for interpretation of thrombotic risks were based on the review of the published literature where subject-level or matched control assessments are infeasible.
- The 30-day all-cause mortality, however, appears to be lower than rates observed in most historical controls. The control data were based on published literature.
- Although the clinical parameters to identify subjects with baseline anti-fXa activity levels > 75 ng/mL were not predictive, the majority of subjects enrolled into the study had levels > 75ng/mL.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Direct fXa inhibitors such as rivaroxaban and apixaban are approved for reduction in the risk of stroke or systemic embolism.	Life-threatening bleeding associated with anticoagulation with direct fXa inhibitors is a serious condition.
Unmet Medical Need	Reversal agents specific to direct fXa inhibitors are not available. Treatment of life-threatening bleeding associated with fXa inhibitors represents an unmet need.	To address this need, it is necessary to facilitate expedited development of therapeutic products to treat, reverse or control bleeding related to anticoagulation with direct fXa inhibitor
Clinical Benefit	The efficacy of ANDEXXA was evaluated using a surrogate endpoint; change from baseline anti-fXa activity level to nadir levels in two HVS. These HVS studies were randomized inactive placebo controlled studies in healthy volunteers who received rivaroxaban or apixaban in the treatment arms and subsequently received ANDEXXA. In these studies, the reversal of anti-fXa activity was observed as demonstrated by a reduction in the anti-fXa level from baseline to nadir levels.	ANDEXXA is effective in reversing the anti-fXa levels, a PD parameter. The correlation between the surrogate endpoint (PD) on and hemostatic efficacy is unknown. The results from the ANNEXA 4 analysis of the relationship between that change from baseline anti-fXa activity and hemostatic response do not establish such correlation. The preliminary analysis of hemostatic responses from the single arm ANNEXA 4 study in 106 subjects are challenging to interpret given the single-arm nature of the study. Furthermore, data from published literature suggest that hemostatic efficacy may be similar with usual care treatments such as PCC[4].

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	The confirmatory study to evaluate the hemostatic efficacy of ANDEXXA is being conducted through an ongoing study, single arm study, ANNEXA 4. The magnitude of change from baseline of anti-fXa activity were consistent in the HVS and ANNEXA 4 studies. Additional analyses were performed in 108 subjects to assess the relationship between the change in anti-fXa activity to hemostatic outcomes assessed as excellent/good and poor/none. The magnitude of change in anti-fXa activity were similar in subjects irrespective of their hemostatic outcomes. Thus, change from baseline anti-fXa level remains a questionable surrogate endpoint.	A RCT study to further evaluate the treatment effect of ANDEXXA on hemostatic outcomes compared to usual care is necessary given these uncertainties.
Risks	Of the 185 subjects who received one dose of ANDEXXA, 17.8% experienced TEE or ischemic events within 45 days.	The TEE and ischemic rates are higher than the anticipated rates observed in a similar population as noted in the published literature. These risks appear to be higher than the anticipated rates for patients who receive anticoagulation after reversal of

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
	Infusion reactions observed in HVS studies were not observed in ANNEXA 4.	anticoagulation. The mechanism of action of ANDEXXA as related to TFPI inhibition may contribute to these risks.
Risk management	ANDEXXA is associated with the risk of TEE, ischemic events, sudden death, and sudden cardiac death.	Early initiation of anticoagulation may minimize the risk of thrombosis and advice as to initiating anticoagulation at the earliest is to be included in the label. A boxed warning is planned. A PMR study to further evaluate the risk of ANDEXXA may be necessary. A RCT study design is preferred.

V. Post-Marketing Required Studies

- Two studies are under consideration. These studies the UCC and the RCT studies are to serve as confirmatory studies if ANDEXXA were to be approved. An agreement on the design of these studies is yet to be reached but efforts to resolve issues are ongoing at the time of finalization of this memo. Please refer to Section IV.A.1. of this memo.

VI. Regulatory Recommendations

- The reviewer does not recommend accelerated approval of ANDEXXA for the following reasons:
    - The inability to correlate change from baseline to nadir anti-fXa levels as predictor of hemostatic efficacy. The data from ANNEXA 4 thus far in 106 subjects did not demonstrate a correlation. In the absence of data to correlate anti-fXa activity levels to hemostasis from a) available literature or b) from the available data from ANNEXA 4, the applicant's hypothesis that anti-fXa levels correlate with hemostatic outcomes, solely on biologic plausibility is challenging..
    - Furthermore, the absence of control data to assess a trend toward hemostatic efficacy in favor of ANDEXXA in the absence of data in support of anti-fXa levels as surrogate endpoint raises uncertainties regarding the benefit of ANDEXXA for the treatment of bleeding related to rivaroxaban and apixaban.
    - The higher (3-4 fold increase) than anticipated thrombotic risks in the intended population further inflates the reviewer's inability to fully characterize the benefit-risk profile. Per Portola, the number of subjects at risk for bleeding following oral factor Xa inhibitors is estimated to be 90,000 per year. At a rate of thromboembolic or ischemic risk of 17.8%, 16,000 patients may be placed at risk without a clear understanding of the benefit.
    - Reference is also made to the FDA Guidance "Guidance for Industry – Expedited Programs for Serious Conditions – Drugs and Biologics particularly the Section VII.C.1 and Section VII.C.2., which pertain to evidentiary criteria for accelerated approval. The guidance states that
        - Evidence of pharmacological activity alone is not sufficient, that clinical data to support a conclusion that a relationship of an effect on the surrogate endpoint to an effect on the clinical outcome is reasonably likely. Analysis of the available clinical data does not demonstrate such correlation
        - Understanding the relationship between the drug's effect on the surrogate endpoint and disease process – available data from the published literature, do not provide evidence of the impact of anti-fXa activity on the disease process. In cases where such correlation was not available the FDA has relied on clinical benefit endpoints to assess efficacy. For example, the correlation of a specific INR to hemostasis has been particularly challenging. The FDA approval of K Centra (prothrombin complex concentrate, human) for urgent reversal of acquired factor deficiency induced by Vitamin K agonist, was based

on regular approval using a randomized controlled study, with hemostatic outcomes as an endpoint.[2] Epidemiological data to support a target level that predicts for improved hemostatic outcomes are not available. There are no other drugs approved as a reversal agent for the pharmacological class of anti-Xa inhibitors.

- External consultations may be obtained when a paucity of data exists with regard to the relationship between the drug's effect on the surrogate endpoint and the disease (risk of bleeding). Given the limited information in the literature and lack of epidemiological and historical data, consultations from experts were obtained during the review of the original submission. Please refer to the Dr. Faulcon's clinical review memo for the review of consultative memos. The opinions regarding the use of anti-Xa levels for regulatory decision making and the clinical significance on anticoagulation activity and risk of bleeding have been excerpted below:
  - Division of Hematology Products (Office of Hematology and Oncology Products, Center for Drug Evaluation and Research): "If the primary endpoint for regulatory decision making was anti-fXa, therapeutic range of anti-fXa assays has not been established for direct oral factor Xa inhibitors, and anti-fXa levels generally are only reflective of drug levels." "The therapeutic range of anti-fXa assays has not been established for direct oral factor Xa inhibitors. Generally, anti-fXa assays for Xa inhibitors reflect the drug concentration and are not thought to reflect the drug's anticoagulation activity."
  - Division of Cardiovascular and Renal Products, Office of Drug Evaluation I, Office of New Drugs, Center for Drug Evaluation and Research): "We are unable to address the clinical significance of the nadir levels of anti-FXa activity or the target level of anti-FXa activity and the risk of bleeding."

- Given that the clinical development paradigm for ANDEXXA is similar to idarucizumab, the reviewer considered whether the regulatory precedence could be weighed in support of a regulatory decision for ANDEXXA under the accelerated approval pathway. Notable differences between the clinical development program and safety findings include: The surrogate endpoints for idarucizumab included measure of activity that represent multiple points along the coagulation cascade: Ecarin clotting time, direct thrombin time and activated plasma thromboplastin time. The surrogate endpoint for the development of ANDEXXA relies solely on anti-fXa levels. The results of the study of idarucizumab showed a sustained reversal of all three surrogate endpoints for at least 72 hours as opposed to transient duration with an immediate increase in anti-fXa levels following completion of the ANDEXXA infusion. Biomarker evidence of procoagulant activity such as increase in thrombin generation was not observed as opposed to observed increase in the thrombin generation, D-dimers, F1+F2 and effect on TFPI with ANDEXXA.[1] The absence of thrombin generation may explain the observed

thromboembolic rates (4.5%) in the bleeding cohort with idaricuzumab (Appendix C). The elevation in the numerous biomarkers of procoagulant activity may provide an explanation for the thromboembolic events observed with ANDEXXA.

Thus, the reviewer has taken the a) evidentiary standards for accelerated approval b) the clinical data from the ANNEXA 4 study to evaluate the relationship between the anti-fXa levels and hemostasis c) the regulatory precedence in cases where the uncertainties regarding the effect of the surrogate and disease outcomes exist d) the risk benefit assessment particularly the inability to elicit preliminary evidence of benefit that isolates the treatment effect of ANDEXXA in the context of the substantial concerns of thrombo-embolic risk, ischemic and mortality risks. These reasons form the basis for the reviewer's recommendation that the applicant complete the clinical studies in the intended population, with the recommendation to consider the option of RCT to evaluate hemostatic efficacy of ANDEXXA as compared to usual care, given that it may be the optimal study design option to assess hemostatic efficacy. If an RCT is not a consideration as a pre-marketing study to demonstrate efficacy of ANDEXXA, the reviewer recommends that the UCC study design and analysis plans should be optimized to minimize the risk of bias with the caveat that in the absence of substantial improvement in the magnitude of hemostatic efficacy of ANDEXXA as compared to usual care cohort, the impact of bias on the outcomes and overall hemostatic efficacy from ANDEXXA may be challenging to interpret.

VII. Literature References

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Appendix A: 14-505 Study Protocol

The summary of the ANNEXA 4 study protocol version 4, dated January 6, 2017 is provided below. This protocol does not include agreements to increase the sample size of the ICH population as provided in the applicant's communication dated May 5, 2017 under IND 15089.

Study Design

ANNEXA -4 is an open-label study of ANDEXXA in subjects receiving fXa with acute major bleeding. The study is ongoing.
120 study sites
First subject was enrolled on June 10, 2015
Data cut-off: April 20, 2017

Key inclusion criteria

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

a. 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.
b. 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.
c. Acute symptomatic bleeding in a critical area or organ, such as retroperitoneal, intra-articular or pericardial, intracranial or intramuscular with compartment syndrome.
d. The patient, for whom the bleeding is intracranial must have undergone a head CT or MRI scan demonstrating the intracranial bleeding.
e. The patient received or was believed to have received either apixaban, rivaroxaban, edoxaban or enoxaparin within 18 hours prior to ANDEXXA administration.

Key exclusion criteria

a. For ICH subjects, GCS <7, intracerebral hematoma volume > 60 cc as assessed by CT or MRI
b. History of TEE or DIC within 2 weeks prior to screening
c. PCC, rfVIIa, blood products within 7 days of screening

Endpoints

Primary Efficacy Endpoints

a. Percent change from baseline in anti-fXa activity to nadir from 5 minutes following bolus administration to prior to end of infusion
b. Hemostatic efficacy at 12 hours from the end of ANDEXXA infusion

Note: The primary endpoints for the comparative analysis between ANDEXXA and usual care have yet to be finalized; therefore, the details of comparative analysis between ANNEXA 4 and UCC studies have not been included.

Secondary Efficacy Endpoint

Relationship between the two primary endpoint to establish change in anti-fXa activity as a predictor of hemostatic efficacy.

Safety Endpoint

30-day survival status
Centrally adjudicated TEEs, EAC-assessed potential thrombotic events
Antibodies to fX and fXa
AEs including preferred terms defined by MedDRA and summarized by organ system class will be provided.

Statistical Analysis Plan

- Safety analysis population: All enrolled subjects who received a dose of ANDEXXA
- Efficacy analysis population: safety-evaluable subjects who were adjudicated by the EAC to have met eligibility and have baseline anti-fXa of at least 75 ng/mL for apixaban and rivaroxaban

Efficacy analysis:
A sample size of 162 subjects to provide 80% power for a two-sided 95% CI above 50% for hemostatic efficacy rate. An anticipated response of 61% is expected.

Safety Monitoring – by an independent DSMB

For details of the study design, please refer to Table 6 of Dr. Faulcon's review memo.

Appendix B: Regulatory interactions during the clinical review of CRL complete response

1) IR request sent on September 29, 2017, requesting 1) for missing datasets for one subject 2) the complete data sets for the safety population of 185 subjects based on the data cut-off date of April 20, 2017, 3) CRFs for all subjects in the safety population 4) AE data table to include death from all causes independent of attribution. The response to this request was provided as Amendment #83 on October 17, 2017.
2) Following review of the response from October 17, 2017, FDA on November 2, 2017, issued an IR requesting that the Applicant provide missing information related to the data sets for the 185 subjects namely missing MedDRA (dictionary-derived) codes, classification of AEs by organ systems and high-level terms. The Applicant's response provided in Amendment #84 on November 7, 2017, included a pdf document providing only dictionary codes without the updated datasets that were requested on November 7, 2017.
3) Following review of the Applicant's response on November 7, 2017, the FDA requested on November 16, 2017, via an IR that the datasets, namely ADAM and SDTM data tables were updated with MedDRA derived codes. The Applicant provided the response to this request as Amendment #90 on December 1, 2017.
4) On December 8, 2017, the Applicant was asked to provide annotated CRFs to which the applicant provided a copy of the annotated CRFs via email. The Annotated CRFs were reviewed and found to be adequate to continue review and audit of the CRFs for safety assessments.
5) Based on the data sets provided on December 1, 2017, the FDA performed the safety analysis to evaluate the risks of thrombotic events with and without anticoagulation, following which the FDA via an IR dated December 10, 2017, requested confirmation of subject IDs who did and did not experience thrombotic events.
6) The Applicant's response dated December 13, 2017 via Amendment 92 noted discrepancies between the summarized data provided in the updated data tables from December 1, 2017 and their December 13, 2017 response. The FDA via an IR dated December 14, 2017, requested listing of patients who received anticoagulation and did not experience a thrombotic event.
7) A response to this IR request was received on December 18, 2017 (submitted on December 15, 2017), Amendment #96, which confirmed that additional subjects not reported to have TEs in the ADAE data sets were noted to have experienced a thrombotic event based on the response from December 15, 2017. Updated ADAE tables were not provided to re-analyze the rate of thrombotic events, risk of thrombosis with and without prophylactic anticoagulation following ANDEXXA exposure and additional supportive safety analyses necessary to complete the review.
8) In an IR dated December 19, 2017, FDA requested further information regarding additional subjects who were noted to have experienced an event in the December 13 and December 15, 2017 responses from the applicant as compared to the ADAE tables submitted to the BLA and an explanation for these discrepancies.
9) The Applicant's response from December 21, 2017 was considered incomplete and generated another IR request on December 21, 2017, requesting explanations for the discrepancies, to provide updated datasets for all subjects who experienced an AE

independent of Endpoint Adjudication Committee (EAC) review and based on investigator assessment, source documents for 6 subjects with discrepant data and one additional subject that the Applicant revised from having experienced a thrombotic event to not having one based on EAC review. The FDA requested a response by December 22, 2017. The applicant requested additional time to provide the response.

10) On December 22, 2017, a letter notifying the Applicant of the Major Amendment (MA), that Amendment 96 was noted to have a substantial amount of new data that would require an additional three months to complete the review. A memo to justify the classification of Amendment 96 as a major amendment was completed by the clinical reviewer. The reasons for the MA include additional time to complete the review as it requires re-analysis of the thrombotic and all-cause mortality, impact of re-initiation of prophylactic and/or therapeutic anticoagulation on thrombotic risks and a comprehensive assessment of benefit-risk to support a regulatory recommendation.
11) On December 27th, 2017 three IR requests were sent requesting a) information as to the location of the Usual Care Cohort Study submission as a Post-Marketing Required (PMR) Study b) total number of screened subjects and enrolled subjects in relation to the 185 subjects in the ADSL dataset and c) request to revise the ADSL dataset to include type of bleeding for each subject that was the basis for meeting study eligibility.
12) An IR request was sent on January 12, 2018, requesting that the ADAE dataset submitted on January 2, 2018, also include MedDRA dictionary codes.
13) An IR request was sent on January 26, 2018, requesting narratives for SAEs and deaths that were listed in the ADAE datasets submitted on January 19, 2018. In addition, a comment was added to note that FDA planned to include in its analysis of AESI, analysis of cardiogenic shock, congestive heart failure, acute respiratory failure specifically those for which alternate causes could not identified. In addition, FDA notified the applicant that one event of iliac artery occlusion and another event of cardiac thrombus were being included as an AESI.

Appendix C: Thrombotic events and all-cause mortality in subjects who require long-term anticoagulation

Trial	Population	Anticoagulant	Rx	Anticoagulation interruption	TEE	All cause mortality	1 yr overall risk	Design	Efficacy outcomes/Other comments
ROCKET AF	AFib w/rivaroxaban-related bleeding	Rivaroxaban	Interuuption of rivaroxaban	5 days	0.36%	Not available	2.2%		
Majeed et al, 2017	ICH (n=59) GI (n=13) other bleeding N=84	Rivaroxaban or apixaban	4 factor PCC	No information 1 of 3 subjects w/TEE was on prophylactic anticoagulation	3.5%	32%* (n=27)		Prospective cohort study	Overall: 69.1% (Successful hemostasis) ICH: 72.8% GIB: 60%
Witt et al, JAMA 2012		Warfarin reversal		Resumed warfarin therapy[α] (median 4 days) (n=260)±	0.4%	11.8%			Retrospective
				Did not resume warfarin (n=180)	5.5%				
Classen et al, 2008	ICH (n=52).	Warfarin		Resumed warfarin (n=23)	4%	48% at 1 year.			Prospective. Most TEE events

Trial	Population	Anticoagulant	Rx	Anticoagulation interruption	TEE	All cause mortality	1 yr overall risk	Design	Efficacy outcomes/Other comments
	Follow-up (n=48)			Did not resume warfarin (n=25)	20%				occurred within 6 month. TEE for warfarin and no warfarin group is 3.5%
Praxbind	Bleeding subgroup (n=66) ICH n= 24 (36%) GIB n=27 (41%)	Dabigatran		5 days (median) in bleeding cohort and 1 day in the surgery cohort.	Bleeding cohort: 3 of 66 (4.5%) Surgery 2/57 (3.5%)	26/123[δ] 19.6% in the sub-group with severe bleeding		Prospective study	

Appendix D-Subject listing of Deaths and FDA-AESI

Deaths -Subjects who died and experienced FDA-AESI

USUBJID N=10	BLEED TYPE	AGE	SEX	FDA AE assessment	DAYS POST ANDEXXA INFUSION	DEATH DATE	FXA	AEDECOD
(b) (6)	ICH	79	M	Sudden cardiac death	15	(b) (6)	Rivaroxaban	Cardiac arrest
	ICH	73	M	Ischemic stroke	7		Rivaroxaban	Subdural empyema
	ICH	95	F	Ischemic stroke	2		Rivaroxaban	Ischemic stroke
	ICH	75	F	Acute respiratory failure	4		Apixaban	Respiratory failure
	Other	88	F	Ventricular tachycardia	6		Apixaban	Ventricular tachycardia
	Other	88	F	Pulmonary embolism	20		Apixaban	Pulmonary embolism
	Other	88	F	Cardiac thrombus	21		Apixaban	Atrial thrombosis
	Other	88	F	Deep venous thrombosis	21		Apixaban	Deep vein thrombosis
	Other	88	F	Cardiogenic shock	21		Apixaban	Cardiogenic shock
	Other	88	F	Cardiac thrombus	21		Apixaban	Cardiac ventricular thrombosis
	GI	86	M	Congestive heart failure	4		Apixaban	Pulmonary edema
	ICH	84	F	Cardiogenic shock	17		Apixaban	Cardiogenic shock
	Other	84	F	Acute myocardial infarction	2		Apixaban	Acute myocardial infarction
	ICH	64	F	Ischemic stroke	11		Apixaban	Infarction
	ICH	82	M	Congestive heart failure	35		Apixaban	Pleural effusion

*Subject (b) (6) experienced multiple FDA-AESI

Death – Subjects who did died but not experience FDA-AESI

USUBJID (n=15)	BLEED TYPE	AGE (YEARS)	SEX	DEATH DATE	FXA
(b) (6)	GI	66	M	(b) (6)	Apixaban
	ICH	80	M		Rivaroxaban
	GI	87	F		Apixaban
	GI	70	M		Rivaroxaban
	GI	82	M		Apixaban
	Other	73	M		Rivaroxaban
	ICH	80	M		Apixaban
	ICH	84	M		Apixaban
	ICH	86	F		Rivaroxaban
	ICH	84	F		Rivaroxaban
	GI	89	M		Apixaban
	Other	93	F		Apixaban
	ICH	77	F		Rivaroxaban
	ICH	96	F		Apixaban
	ICH	89	F		Apixaban

Appendix E-Subjects who either died or experienced an FDA-assessed AESI and were anticoagulated

Subject ID	Bleed type	FDA-AESI	Death	Anticoagulated Before	Anticoagulated After
(b) (6)	Other	No	Y	N	Y
	ICH	No	Y	N	Y
	ICH	No	Y	N	Y
	ICH	No	Y	N	Y
	ICH	No	Y	N	Y
	GI	No	Y	N	Y
	ICH	No	Y	Y	N
	ICH	N	Y	Y	N
	GI	Y	N	Y	N
	ICH	Y	N	Y	N
	ICH	Y	N	Y	N
	ICH	Y	N	Y	N
	ICH	Y	N	Y	N
	Other	Y	N	Y	N
	ICH	Y	N	Y	N
	ICH	Y	N	Y	N

Subject ID	Bleed type	FDA-AESI	Death	Anticoagulated Before	Anticoagulated After
(b) (6)	ICH	Y	N	Y	N
	ICH	Y	N	N	Y
	ICH	Y	N	N	Y
	GI	Y	N	N	Y
	ICH	Y	N	N	Y
	Other	Y	N	N	Y
	ICH	Y	N	N	Y
	Other	Y	N	N	Y
	Other	Y	N	N	Y
	GI	Y	N	N	Y
	ICH	Y	N	N	Y
	GI	Y	N	N	Y
	GI	Y	N	N	Y

Appendix F-FDA adjudication of safety events following IR response of 02/26/18

Subject ID	Data set entry	Summary of Applicant's comments from IR response 02/26/18	FDA comments	FDA disposition
(b) (6)	DVT per CSR, not reported in ADAE dataset	Erroneous reporting of DVT. Right lower extremity swelling was confirmed as hematoma and evacuated by surgical procedure. No DVT per duplex imaging (7 days post-ANDEXXA)	None. Duplex report reviewed	Agree with Applicant – no DVT. Subject will be excluded from the TEE/FDA-AESI analyses.
(b) (6)	Troponin elevated for 24 hours	Elevated troponins were observed at three consecutive assessments over 24 hours, beginning 11 hours post infusion. EKG showed non-specific ST and T wave abnormalities unchanged from pre-treatment EKG. Cardiology consultant did not recommend any further work-up.	Isolated but elevated troponin within 12 hours of ANDEXXA is considered attributable to the ANDEXXA and a cardiac ischemic event. Subject had underlying CAD.	Subject will be included in the TEE/FDA-AESI analyses.
(b) (6)	Ventricular tachycardia (VT)	Telemetry noted 7 beat run of VT. Interrogation of the ICD did not confirm non-sustained VT but noted premature ventricular contractions (PVCs)	Agree with Applicant, and based on the ICD interrogation that VT is unlikely to have occurred.	Subject will be excluded from the TEE/FDA-AESI analyses.
(b) (6)	Sudden Death	Unwitnessed, no further information is available.	The sudden death is	Subject will be included in the

Subject ID	Data set entry	Summary of Applicant's comments from IR response 02/26/18	FDA comments	FDA disposition
			attributable to ANDEXXA.	TEE/FDA analyses.
(b) (6)	Respiratory failure	Underlying history of CAD, COPD, CKD. Readmitted 8 days following ANDEXXA infusion, with acute shortness of breath and wheezing. D-dimer elevated (2.5 µg/mL), without troponin elevation, chest Xray suggestive of congestive heart failure. V/Q scan – low probability of pulmonary embolism, responded to nebulizer and diuretics and corticosteroids.	Agree with applicant, that based on the low probability V/Q scan, response to diuretics and COPD management, Elevated D-dimers noted in this subject could be explained by renal impairment.	Subject will be excluded from the TEE/FDA analyses.
(b) (6)	Subdural empyema	Subject presented with right occipital hemorrhage on CT. MRI imaging following ANDEXXA infusion suggested that right occipital hemorrhage may represent hemorrhagic transformation of a prior infarct. However, the MRI also noted acute infarct in the frontal cortex and right frontal subdural hematoma. Subsequent MRI noted that subdural collections were increasing in size and consistent with subdural empyema. Subject was also noted to have fever and leukocytosis.	The MRI finding of acute frontal lobe cortical infarct is attributable to ANDEXXA as this event was first noted following ANDEXXA infusion.	This subject will be included in the TEE/FDA-AESI analysis.
(b) (6)	Congestive heart failure	Subject was discharged 11 days post-ANDEXXA and readmitted without response to diuresis and subsequently treated for pneumonia with antibiotics and recovered.	Agree with the applicant that the likely cause of	Exclude subject from

Subject ID	Data set entry	Summary of Applicant's comments from IR response 02/26/18	FDA comments	FDA disposition
			cardiac and respiratory decompensation was related to pneumonia.	TEE AESI analysis.
(b) (6)	Ventricular tachycardia	Extensive cardiac history and dual-chamber pacemaker which was interrogated and did not confirm the telemetry finding of Vtach.	Agree with Applicant that Vtach was an unlikely event.	Exclude subject from TEE/AESI analysis.
(b) (6)	Acute respiratory distress	Acute respiratory distress that occurred within 24 hours of ANDEXXA infusion requiring intubation. CT and ultrasound scans were negative for DVT/PE. Subject had a second episode of acute respiratory distress 13 days after infusion that required another intubation. No mention of work-up for cardiac ischemic etiology.	Unable to rule out cardiac ischemia contributed by ANDEXXA as possible etiology of the acute respiratory failure.	Include subject in the TEE/AESI analysis.
(b) (6)	Chest pain	Transient chest pain 3 days post-ANDEXXA, without respiratory decompensation and without elevation of chest pain	Agree with Applicant, chest pain unlikely to be of cardiac etiology.	Exclude subject from TEE/AESI analysis.
(b) (6)	Respiratory failure	Bibasilar rales and rib fractures were noted within 24 hours after admission without respiratory decompensation, requirement for oxygen or other supportive measures.	Agree that the event does not represent respiratory failure.	Exclude subject from TEE/AESI analysis.
(b) (6)	Chest pain	Chest pain associated with EKG changes suggestive of cardiac ischemia and elevated cardiac enzymes that	This event is considered a cardiac ischemic	Include in the TEE/AESI analysis as

Subject ID	Data set entry	Summary of Applicant's comments from IR response 02/26/18	FDA comments	FDA disposition
		occurred 21 days after ANDEXXA infusion. Coronary angiography did not reveal an obstructive cause.	event. The Applicant's diagnosis of digitalis-induced EKG changes is noted.	myocardial infarction.
(b) (6)	Cerebrovascular event	The subject experienced a fall 14 days after ANDEXXA infusion and was noted to have decreasing hematoma (ICH being the index event for study eligibility). Initial CT and subsequent CT imaging did not confirm an infarct.	Agree with the Applicant that the event is not considered an ischemic stroke	Exclude from TEE/AESI analysis. Will be considered change in mental status following a fall.
(b) (6)	Death and multiorgan failure	Subject with ICH developed renal failure, pain in the shoulder (deemed septic joint) without supportive information approximately 2 weeks after ANDEXXA infusion.	The event will be considered a death preceded by acute on chronic renal failure followed by multi-organ failure and death.	Include in the TEE/AESI as renal failure, multi-organ failure and death.

Appendix G-Adverse Events by Body Organ System

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
Blood and Lymphatic System	Anemia	4		
	Coagulopathy		1	
	Heparin-Induced thrombocytopenia	2	1	
	Leukocytosis	2		
	Thrombocytopenia	3		
Cardiovascular	Acute Myocardial Infarction	4	3	
	Atrial fibrillation	6		1
	Atrial thrombosis	1	1	
	Atrioventricular block complete	1	1	
	Bradycardia	2		
	Cardiac arrest	2	1	1
	Cardiac failure congestive	3	2	
	Cardiac ventricular thrombosis	1	1	
	Cardiogenic shock	3	1	2
	Cardiopulmonary failure	1		
	Cardio-respiratory arrest	1	1	
	Myocardial infarction	1		
	Pericarditis	1		
	Sinus node dysfunction		1	
	Systolic dysfunction		1	
	Tachycardia	2		
	Ventricular tachycardia	3		
	Prolonged QT interval	1		
Ear and Nose	Deafness	1		
Endocrine	Euthryoid Sick Syndrome	2		

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
	SIADH	1		
Gastrointestinal				
	Abdominal pain	2		
	Anal sphincter atony	1		
	Barrett's Esophagus	1		
	Constipation	2		
	Dental caries	1		
	Diarrhea	1		
	Dry mouth	1		
	Dyspepsia	1		
	Dysphagia	5	1	
	Fecal incontinence	2		
	Gastritis	1		
	Gastrointestinal hemorrhage	2	1	
	Hematochezia	1		
	Hemorrhoids	1		
	Ischemic hepatitis	1	4	
	Large intestine polyp	1		
	Melena	1		
	Nausea	3		
	Esophagitis	1		
	Rectal hemorrhage	2		
	Vomiting	3		
	Catheter site haematoma	1		
	Chest discomfort	1		
	Chest pain	7	1	
	Device leakage	1		
	General physical health deterioration	3	1	
	Hyperthermia	2		
	Multi-organ failure	2		2
	Edema	5		
	Pyrexia	7		

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
	Sudden cardiac death	1		1
	Sudden death	1		1
	Swelling	1		
Infections	Arthritis bacterial			
	Bronchitis			
	Cellulitis	3	1	
	Clostridium difficile infection	1		
	Herpes zoster	1		
	Lower respiratory tract infection	1		
	Oral candidiasis			
	Pneumonia	11	4	3
	Postoperative wound infection	2		
	Respiratory tract infection			
	Sepsis	7	5	2
	Serratia bacteraemia	1	1	
	Subdural empyema	1		5
	Upper respiratory tract infection	2		
	Urinary tract infection	20	3	
	Arthritis bacterial			
	Bronchitis			
	Cellulitis			
	Clostridium difficile infection			
Injury and Poisoning	Fall	3	1	
	Dural tear	1		
	Subdural hematoma	1		
	Verterbral fracture	1	1	

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
Investigations	Blood phosphorus decreased	1		
	Blood thyroid stimulating hormone	1		
	Hemoglobin decreased	1		
	Hemoglobin decreased	1		
	Oxygen saturation decreased	1		
	Platelet count decreased	1		
	Transaminases increased	1		
	Transaminases increased	1		
	Urine Output decreased	1		
Metabolism and nutrition disorders	Diabetes mellitus inadequate control	1		
	Fluid overload	1		
	Hyperglycemia	1		
	Hypernatremia	2		
	Hypocalcemia	1		
	Hypoglycemia	1		
	Hypokalemia	4		
	Hypomagnesemia	2		
	Hyponatremia	3	1	
	Hypophagia	1		
	Metabolic acidosis	1		
Neoplasm	Brain neoplasm	1	1	
Nervous System	Anosmia	1		
	Basal ganglia hemorrhage	1	1	
	Brain edema	2	2	

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
	Brain edema			
	Cerebral hemorrhage	2	1	1
	Cerebral hemorrhage	4	4	
	Cerebral infarction	3	3	
	Cerebral infarction	1		
	Cerebral infarction			
	Cerebral infarction			
	Cerebrovascular accident	3	3	
	Dementia	1		
	Depressed level of consciousness	1	1	
	Dizziness	1		
	Embolic stroke	1		
	Encephalopathy	2	2	
	Epilepsy	1		
	Extrapyramidal disorder	1		
	Hemorrhage intracranial	1	1	
	Headache	8	3	
	Intracranial venous sinus thrombosis	1	1	
	Intraventricular hemorrhage	1		
	Ischemic stroke	3	1	1
	Neurological decompensation	1		
	Paresthesia	1		
	Seizure	5		
	Subarachnoid hemorrhage	1		
	Syncope	1		
	Agitation	2		
	Bradyphrenia*	1		
	Delirium	3		
	Depression	2	3	
	Insomnia	2		

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
	Mental status changes	5	2	
	Suicidal ideation	1		
	Acute kidney injury	6	1	
	Hematuria	3		
	Incontinence	1		
	Nephrotic syndrome	1	1	
	Neurogenic bladder	1		
	Urinary retention	4		
Pulmonary	Acute pulmonary edema	1	1	
	Acute respiratory failure	3	3	
	Apneic attack	1	1	
	Aspiration	1	1	
	Atelectasis	1		
	Bronchial secretion retention	1	1	
	Chronic obstructive pulmonary disease	1	1	
	Dyspnea	3		
	Epistaxis	3		
	Hypoxia	1	1	
	Orthopnea	1	1	
	Pleural effusion	2		1
	Productive cough	1		
	Pulmonary embolism	5	5	
	Pulmonary edema	1	1	
	Rales	1		
	Respiratory distress	1	1	
	Respiratory failure	5	3	2

AE Body System (n=185 subjects)	AE Type (n=122 events)	All Grades	Grade 3-4	Grade 5
Skin and subcutaneous tissue disorders	Decubitus ulcer	1		
	Erythema	1		
	Ingrowing nail	1		
	Pruritus	1		
	Rash	3		
Surgical and medical procedures	Sinus operation	1		
	Tracheostomy	1	1	
	Ventricular drainage	1	1	
Vascular disorders	Arteriosclerosis	1		1
	Deep vein thrombosis	11	2	
	Hematoma	4	1	
	Hemorrhage	2	2	
	Hypertension	1		
	Hypertensive crisis	1		
	Hypotension	8	2	
	Iliac artery occlusion	1		
	Infarction	1		1
	Peripheral arterial occlusive disease	1		

*Bradyphrenia: Slowness of thought

The applicant's ADAE data set did not include dictionary-derived terms for 2 subjects ((b) (6) and (b) (6) – Subject (b) (6) had two low level AE terms included in the AE table; intermittent Afib (Grade 1) and intermittent urine output (Grade 1). For FDA analyses, intermittent Afib was grouped as atrial fibrillation and intermittent urine output was grouped as urinary retention for Subject (b) (6) . For Subject (b) (6) , prolonged QT noted on EKG was noted as an AE low level term, and was analyzed as such.

Grouped Terms

Anemia: Anemia and Iron deficiency Anemia

Acute Myocardial Infarction: Acute Myocardial Infarction, myocardial infarction and troponin increase

Deep vein thrombosis: Deep vein thrombosis, Embolism venous and Venous thrombosis limb
SIADH: Syndrome of Inappropriate Anti-diuretic Hormone
Abdominal pain: Abdominal pain and Abdominal pain lower
Edema peripheral: Edema and Edema peripheral
Pneumonia: Pneumonia and aspiration pneumonia
Rash: Rash, Rash pruritic and Genital Rash
Sepsis: Sepsis and septic shock

Appendix H-Phase 3 Healthy Volunteer Studies

Trial ID (Type of	Design	Subjects; Mean Age	Anticoagulant Administratio	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	n=24 400 mg bolus	n=9
			Part 2: Apixaban (n=32) 5 mg orally	n=24 400 mg bolus followed by a 120 min infusion at 4	n=8
14-504 Efficacy / Safety	Single center, randomized, double-blind, placebo-	n=80 healthy older subjects; 56 years (50–	Part 1: Rivaroxaban (n=41) 20 mg orally every 24 hours	n=27 800 mg bolus	n=14