Application Type	Original Application
STN	125586/0
CBER Received Date	December 18, 2015 (original submission) August 4, 2017 (response to CR letter)
PDUFA Goal Date	May 5, 2018
Division / Office	DPPT /OTAT
Committee Chair	Mikhail Ovanesov, Ph.D.
Clinical Reviewer(s)	Bindu George, M.D.
Project Manager	Jean Gildner
Priority Review	Yes
Reviewer Name(s)	Chunrong Cheng, Ph.D.
Review Completion Date / Stamped Date	April 13, 2018
Supervisory Concurrence	Renee C. Rees, Ph.D., Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, Ph.D. Chief, Therapeutics Evaluation Branch
	John Scott, Ph.D., Acting Director, Division of Biostatistics
Applicant	Portola Pharmaceuticals
Established Name (Proposed) Trade Name	Coagulation Factor Xa (Recombinant), Inactivated ANDEXXA
Formulation(s), including Adjuvants, etc	Water for Injection, diluent; Polysorbate 80, additive; Sucrose, additive; Mannitol, additive; Hydrochloric acid, additive; Arginine hydrochloride, additive
Dosage Form(s) and Route(s) of Administration	Lyophilized powder with nominal dose of 100 mg, IV
Dosing Regimen	The lower dose regimen consists of an initial bolus of 400 mg followed by a 2-hour infusion of 480 mg of the product, totaling 880 mg. The higher dose regimen consists of an initial bolus of 800 mg followed by a 2-hour infusion of 960 mg, totally 1760 mg.
Indication(s) and Intended Population(s)	For patients treated with Factor Xa inhibitors, rivaroxaban and apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding

APPROVED
By Chunrong Cheng at 2:43 pm, Apr 13, 2

APPROVED
By Renee C Rees at 2:47 pm, Apr 13, 2018

APPROVED
By Boguang Zhen

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1. Executive Summary

ANDEXXA is a recombinant modified human fXa protein indicated for subjects treated with fXa inhibitors, rivaroxaban and apixaban, when reversal of anticoagulation is needed in life threatening or uncontrolled bleeding.

The original BLA was submitted under the Accelerated Approval pathway in December, 2015, including two completed Phase 3 studies (14-503 and 14-504) in healthy volunteers and one ongoing Phase 3b/4 study ANNEXA-4 (14-505) in acute bleeding subjects. Both Phase 3 studies met their study success criterion: significantly greater anti-fXa activity reduction was observed in subjects in the ANDEXXA group compared to the placebo group. For example, in Part 1 of Study 14-503, the mean percent change of anti-fXa activity from baseline to the nadir was -93.86% (±1.65%) for the ANDEXXA group and -20.71% (±8.56%) for the placebo group (p<0.0001). In the ongoing Study 14-505, 52 subjects were available and evaluable for hemostatic efficacy analysis.

A Complete Response Letter (CRL) was issued on August 17, 2016, mainly due to Chemistry, Manufacturing, and Controls (CMC) issues. One statistical comment regarding data inconsistency in Study 14-504 was included in the CRL and the applicant provided their response to the statistical CR item on August 4, 2017, which I reviewed and found acceptable. In addition, based on FDA's request, updated datasets with a cut-off date of April 20, 2017 for Study 14-505 were submitted on October 17, 2017. These datasets included a total of 185 subjects, 108 of whom were eligible for efficacy analysis. However, 17 of the 108 subjects had their efficacy outcome pending or non-evaluable. Upon FDA's request, the applicant provided updated analyses on these 91 subjects.

- For hemostatic efficacy, 82.42% (75/91) of the subjects achieved "excellent" or "good" outcome, and the results were overall consistent across fXa inhibitor and primary bleed type. The 95% confidence interval (CI) is 73.02%-89.60%.

- For the change in anti-fXa activity over time, most subjects displayed a pattern similar to that seen in healthy volunteers (e.g., Studies 14-503, 14-504) with a rapid reduction followed by a gradual increase. This pattern was similar among subjects with "excellent" or "good" hemostatic efficacy and subjects with "poor/none" hemostatic efficacy.

I confirmed the above results. However, because the study is still ongoing, the clinical team hasn't verified the adjudication of hemostatic efficacy outcome for each individual subject. In addition, due to the lack of a control arm, the efficacy results should be interpreted cautiously. There are no outstanding statistical issues associated with this BLA.

2. Clinical and Regulatory Background

Direct and indirect fXa inhibitors are associated with an increase in bleeding events, some of which are life-threatening or fatal. Currently there are no products approved to serve as an antidote to direct and indirect fXa inhibitors. IND 15089 for ANDEXXA was submitted to the FDA in 2012. It was designated a Breakthrough Product for an unmet medical need in 2013, and was given Orphan Drug status in 2015. When the BLA was originally submitted, the proposed indication was for subjects treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as:

- Life-threatening or uncontrolled bleeding

- (b) (4)

A statistical review memo was completed on July 26, 2016 and a CRL was issued on August 17, 2016, mainly due to CMC issues. It also included clinical issues regarding the design of Study 14-505 and one statistical comment (Q18) regarding data inconsistency in Study 14-504.

A Type A meeting (CRMTS 10481) was held on October 27, 2016 to discuss a regulatory pathway to provide the second generation ANDEXXA product. In addition, FDA provided some important clinical comments in the meeting minutes as summarized below:

- FDA expressed no objection to a proposed indication that is limited to reversal of the anticoagulant effect of rivaroxaban and apixaban, as it would likely facilitate marketing approval. If ANDEXXA were to receive marketing approval, additional data of ANDEXXA to reverse the anticoagulant effects of (b) (4) could be submitted via an efficacy supplement.

- FDA agreed that the results of the ANNEXA-4 and Usual Care Cohort (UCC) Studies could be sufficient for marketing approval of ANDEXXA. However, FDA's review of the resubmission, particularly the safety database, may identify additional issues that would need to be addressed prior to marketing approval.

- Initial enrollment of subjects into the UCC Study would be important as evidence of Portola's commitment to completing a confirmatory study.

Note: The protocol of the UCC study (16-510) and the Statistical Analysis Plan (SAP) for ANNEXA-4 were submitted on June 30, 2017 under 15089/191. No major statistical issues were identified.

In the BLA resubmission received on August 4, 2017 (Amendment 77), the indication was revised for subjects treated with an fXa inhibitor (apixaban or rivaroxaban) when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. However, the applicant provided additional data to support the possible inclusion of enoxaparin and edoxaban in the label.

On February 16, 2018, FDA issued a letter under IND 15089 stating that:

- Both the UCC and ANNEXA-4 studies have limitations that can potentially introduce bias, which may limit the interpretation of the efficacy of ANDEXXA.

- To minimize bias introduced in cross-study comparisons, a blinded randomized controlled trial (RCT) may be necessary. FDA encouraged the applicant to submit to IND 15089 a protocol and statistical analysis plan (SAP) for an RCT. FDA had not yet determined whether the results of the RCT will be necessary prior to marketing approval. However, FDA believed that reaching agreement on the design of the RCT would facilitate our assessment of the approvability of your BLA.

- FDA believed the UCC and ANNEXA 4 studies would provide data supportive of the RCT study for a marketing application.

As a result of above request, the applicant submitted a draft RCT protocol to evaluate the effect of ANDEXXA versus usual care on the rate of effective hemostasis under BLA 125586/0.115. FDA provided clinical and statistical comments on the protocol, which were discussed in the Type A meeting held on March 23, 2018. Responses to those comments and a revised protocol were received on March 30, 2018 (IND 15089/216), which are currently under review.

In this review memo of the resubmission, the two completed Phase 3 studies (14-503 and 14-504) on healthy volunteers are summarized in Section 3. The statistical item in the CRL for Study 14-504 is included in this section as well.

Study 14-505 is reviewed in Section 4. As submitted in the Day 180 update (Amendment 38), 52 subjects were available and evaluable for hemostatic efficacy analysis with the data cutoff date of June 9, 2016. In the resubmission, with the data cutoff date of September 20, 2016, 101 subjects were included in the Complete Safety Population, 74 of whom were included in the Complete Efficacy Population. In addition, an addendum was included in the resubmission with some updated efficacy and safety results as of April 20, 2017, with no datasets associated. These results were used in a Data Safety and Monitoring Board (DSMB) meeting and safety report. Based on a request from the clinical and statistical reviewers, the applicant submitted SAS datasets on October 17, 2017 (Amendment 83), and submitted additional analyses on December 13, 2017 (Amendment 93). The most recent analyses performed by the applicant are presented in Section 4.3, and my analyses are presented in Section 4.4. The analyses on datasets with an earlier cutoff date are not included in this review, but they had similar results as the recent datasets.

Amendment 96 was considered as a Major Amendment, which extended the action due day to May 4, 2018.

3. Summary of Studies 14-503 and 14-504
(see review memo dated on 7/26/16 for detailed results)

Study 14-503 and Study 14-504 were Phase 3, randomized, double-blind, placebo-controlled, 2-part studies to assess the ability of ANDEXXA to reverse anticoagulation by apixaban (Study 14-503) or rivaroxaban (Study 14-504) at the doses and regimens selected. Both studies were conducted in older (50-75 years) healthy subjects dosed to steady-state with apixaban or rivaroxaban.

- Study 14-503 (apixaban): 34 subjects enrolled into Part 1 (25 subjects with ANDEXXA 400 mg bolus, 9 placebo) and 32 subjects enrolled into Part 2 (24 subjects with ANDEXXA 400 mg bolus plus 4 mg/min 120 minute infusion, 8 placebo)

- Study 14-504 (rivaroxaban): 41 subjects enrolled into Part 1 (27 ANDEXXA with 800 mg bolus only, 14 placebo;) and 39 subjects enrolled into Part 2 (26 ANDEXXA with 800 mg bolus plus 8 mg/min 120 minute infusion, 13 placebo)

The results of the primary efficacy endpoint, mean percent change from baseline in anti-fXa activity at the nadir, are summarized as follows. The p-value was < 0.0001 for all comparisons to the placebo.

- A bolus of ANDEXXA rapidly (within 2–5 minutes) reduced anti-fXa activity to a greater extent than placebo in subjects receiving apixaban (93.86% [± 1.65 Standard Deviation (SD)] vs. 20.71% [± 8.56]) or rivaroxaban (92.22% [± 10.70] vs. 18.39% [± 14.66]). After completion of the ANDEXXA bolus, reversal of anti-fXa activity persisted for 2 hours.

- When administered as a bolus plus a 2-hour infusion, ANDEXXA also reduced anti-fXa activity to a greater extent than placebo at the end of infusion in subjects on apixaban (92.34% [± 2.81] vs. 32.70% [± 5.58]) or rivaroxaban (96.72% [± 1.84] vs. 44.75% [± 11.75]). Reversal of anti-fXa activity with ANDEXXA persisted for 1 to 2 hours after completion of the infusion, depending on the anticoagulant received, followed by return to placebo levels.

- All ANDEXXA-treated subjects had at least 80% reversal of anti-fXa activity, except for 1 subject who did not receive the full dose of ANDEXXA due to a malfunction with the IV administration, compared to none of placebo-treated subjects.

In both studies, ANDEXXA was well tolerated with no serious adverse events (AEs), severe AEs, withdrawals from the study due to AEs, thrombotic events (TEs), or antibodies to fX or fXa detected. One subject with a history of hives was discontinued from ANDEXXA 35 minutes into the infusion after developing erythematous hives, which resolved after treatment with a single oral dose of diphenhydramine.

Response to a CRL statistical item

The only statistical item included in the CRL is for part 1 of Study 14-504. The modified Intention-to-Treat (mITT) set included 14 subjects for the placebo group; however, only 13 subjects were included in the primary analysis. The applicant explained in the resubmission that this subject had out-of-window samples at the +2 minute and +5 minute time points after the completion of the ANDEXXA bolus and did not enter the nadir analysis according to the pre-specified SAP. Sensitivity analysis imputing 0% for this subject yielded very similar results. The response is acceptable.

4. Review of ANNEXA-4 (14-505)

4.1. Design Overview

This is a multicenter, prospective, open-label, Phase 3b/4 study of ANDEXXA in subjects presenting with acute major bleeding who have recently received one of the following fXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. A minimum of approximately 110 evaluable subjects with intracerebral hemorrhage (ICH) will be enrolled in the study.

Once the informed consent form (ICF) is signed and eligibility is confirmed, subjects will receive ANDEXXA as an intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. The start of the ANDEXXA bolus must be within 18 hours following the last dose of fXa inhibitor, if the timing of the last dose is known. If the timing of the last dose of fXa inhibitor is unknown, the ANDEXXA infusion must begin no later than 3 hours following the signing of the ICF.

There are two possible dosing regimens as described below.

- Subjects receiving apixaban and those subjects who received rivaroxaban >7 hours ago: 400 mg bolus + 480 mg continuous infusion

- Subjects receiving enoxaparin, edoxaban, or a dose of rivaroxaban within ≤ 7 hours or at an unknown time: 800 mg bolus + 960 mg continuous infusion

Baseline is defined as the most recent assessment prior to the start of the ANDEXXA bolus. For post-baseline assessments, time 0 is defined as the end of the continuous ANDEXXA infusion. Re-dosing may be administered when specific criteria are met.

Subjects will be evaluated for the primary hemostatic efficacy endpoints for 12 hours from the end of ANDEXXA infusion with clinical and imaging assessments for bleeding. Hemostatic efficacy will be adjudicated by an independent Endpoint Adjudication Committee (EAC). The EAC will also adjudicate whether subjects met inclusion criteria, re-bleeding events, deaths, potential TEs, and AEs of special interest. All AEs will be followed through the Day 30 post-treatment visit.

4.2. Statistical Considerations & Statistical Analysis Plan

The following two primary endpoints will be analyzed:

- The percent change in anti-fXa activity from baseline to the nadir from the evaluation period (where the evaluation period starts 5 minutes following the end of the ANDEXXA bolus and ends 10 minutes after the end of the ANDEXXA infusion),

- The achievement of hemostatic efficacy (excellent, good, or poor/none).

For percent change in anti-fXa activity, subjects who do not have at least one anti-fXa activity level within the evaluation period for non-administrative reasons will have percent decrease imputed as 0.0%.

The Efficacy Analysis Population will include all enrolled subjects who: 1) receive any amount of ANDEXXA treatment; 2) are determined by the EAC to meet the bleeding entry criteria; and 3) have a baseline anti-fXa level of at least 75 ng/mL (0.25 IU/mL for subjects receiving enoxaparin).

The Safety Analysis Population will consist of all subjects enrolled and treated with any amount of ANDEXXA.

4.3. Efficacy results on datasets with a cutoff date of April 20, 2017, applicant's analyses

Because the applicant did not present their efficacy analyses when submitting the datasets, FDA sent out the following request on December 6, 2017:

Please provide the following analyses to the FDA by COB Friday, December 8, for ANNEXA-4 (Study 14-505), based on the 108 efficacy evaluable subjects, in the most recent datasets with the cut-off date of April 20, 2017.

- *Item 1: A table of hemostatic efficacy by fXa inhibitor and primary bleed type. Please note that in the figures, each individual subject should have one line, rather than a single line of the median.*

- *Item 2: Figures for the time course of anti-fXa activity by fXa inhibitor and primary bleed type. Please note that in the figures, each individual subject should have one*

line, rather than a single line of the median. To be included in the figures, subjects should have data available for baseline, 5 minutes after bolus, end of infusion, and 4 hour assessment, but are allowed to have a missing measurement for the 8 hour and/or 12 hour assessments.

- *Item 3: Same figures as above (item #2), but stratified by the hemostatic efficacy categories "excellent/good" or "poor/none."*

The analyses were provided on December 13, 2017 (Amendment 93) and will be presented in the following.

- Item 1: Table 1 lists the hemostatic efficacy, stratified by fXa inhibitor (apixaban, rivaroxaban, enoxaparin) and primary bleed type: intracranial hemorrhage (ICH), gastrointestinal bleeding (GI), and bleeding from other sites. In addition, the applicant provided the mean percent reduction in anti-fXa activity (column 4 of Table 1). Note that the percentage in last column uses the denominator that excludes subjects whose hemostatic outcome was either "not evaluable" or "pending". Overall, 82.42% (75/91, 95%CI [73.02%, 89.60%]) of the subjects achieved "excellent" or "good" outcome.

Table 1. Hemostatic Efficacy Stratified by FXa Inhibitor and Bleed Type in Efficacy Analysis Population (n=108)

FXa Inhibitor	Bleed Type	Number	Mean Reduction in Anti-fXa Activity	Hemostatic Efficacy (Number)				Effective Hemostasis (%)
				Excellent/Good	Poor/None	Not Evaluable	Pending	
Apixaban	ICH	38	91.7	23	5	2	8	82.1
	GI	18	90.0	14	2	2	0	87.5
	Other	5	84.0	4	0	0	1	100.0
Rivaroxaban	ICH	16	86.2	10	4	0	2	71.4
	GI	24	78.9	21	2	0	1	91.3
	Other	5	88.8	2	3	0	0	40.0
Enoxaparin	ICH	1	84.0	0	0	1	0	NA
	GI	1	75.4	1	0	0	0	100.0
	Other	0	NA	NA	NA	NA	NA	NA
Total		108	NA	75	16	5	12	82.4

Source: Table 1.11.3-2 in 14-505 Clinical Information Amendment, 125586/0/93

- Item 2: The results of Item 2 are not presented in this memo as the information is reflected in Item 3.

- Item 3: The reasons for exclusion of subjects from the analyses performed in Item 3 are provided in Table 2 below.

Table 2. Inclusion of Subjects for Item 3

| Dataset/Description	Number of Patients
20 April 2017 data cut	185
Efficacy evaluable patients from 20 April 2017 data cut.	108
Patients analyzed for Item 3	82
Reasons for exclusion:	
Enoxaparin use	1
Missing anti-fXa activity level at one or more of the EOB, EOI, or 4 hour time points	7
Hemostatic efficacy pending adjudication	8
Hemostatic efficacy not evaluable	1
Missing anti-fXa activity level at one or more of the EOB, EOI, or 4 hour time points AND hemostatic efficacy pending adjudication	4
Missing anti-fXa activity level at one or more of the EOB, EOI, or 4 hour time points AND hemostatic efficacy not evaluable	4
Enoxaparin use AND missing anti-fXa activity at one or more of the EOB, EOI, or 4 hour time points AND hemostatic efficacy not evaluable	1

EOB=End of bolus; EOI=End of Infusion
Note: Reasons for exclusion are mutually exclusive.

Source: Adapted from Table 1.11.3-1 in 14-505 Clinical Information Amendment, 125586/0/93

Figure 1 and Figure 2 display the time course of anti-fXa activity by hemostatic efficacy for apixapan and rivaroxaban, respectively. In each figure, A and D are for ICH; B and E are for GI; and C and F are for other bleed types. The first row (A-C) is for subjects with "excellent" or "good" hemostatic outcome; the second row (D-F) is for subjects with "poor/none" hemostatic outcome. The figure for enoxaparin is not presented due to a small number of subjects (n=2).

Figure 1. Change in Anti-fXa Activity in Efficacy Analysis Population Taking Apixapan, by Hemostatic Efficacy
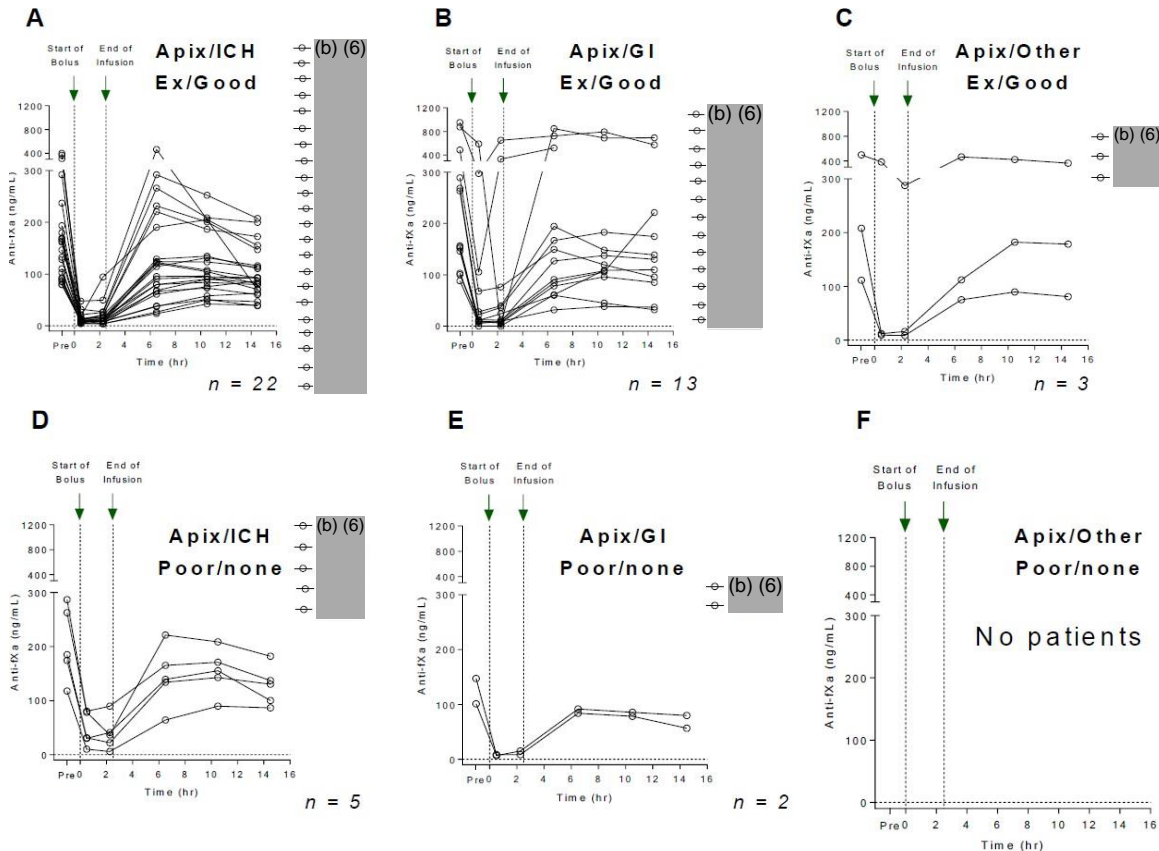
Source: Figure 1.11.3-3 in 14-505 Clinical Information Amendment, 125586/0/93

Figure 2. Change in Anti-fXa Activity in Efficacy Analysis Population Taking Rivaroxaban, by Hemostatic Efficacy
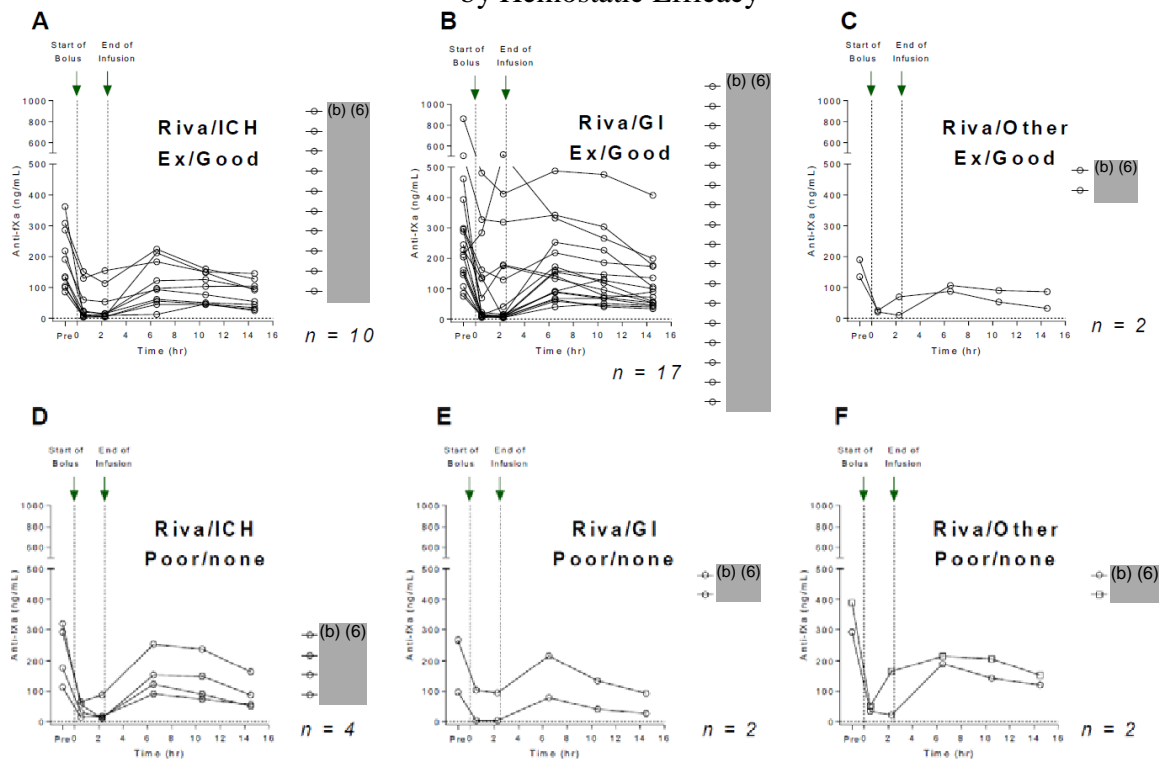
Source: Figure 1.11.3-4 in 14-505 Clinical Information Amendment, 125586/0/93

The applicant provided some discussion of the above results. The major points are summarized below.

- With regard to the change in anti-fXa activity over time, most subjects had a rapid reduction in the anti-fXa activity at the first time point after the bolus, followed by a gradual increase over the 1 to 2 hours after completion of the infusion to a level somewhat lower than the baseline value, then a gradual drop-off thereafter. This pattern was consistently observed when subjects were stratified by either fXa inhibitor or bleed type.

- There were 15 subjects with supra-therapeutic baseline anti-fXa activity levels (> 300 ng/mL). The percentage reduction in these subjects was generally less than the reduction in subjects with lower baseline anti-fXa levels; however, the absolute reductions were simultaneously greater. For 13 of these 15 subjects (86.7%), the hemostatic efficacy was excellent (n=12) or good (n=1). The applicant argued that these data were supportive of the hypothesis that the absolute magnitude of reduction in anti-fXa activity may contribute to the achievement of hemostatic efficacy.

- When the figures were stratified by the achievement of effective hemostasis or not, the subjects with "excellent" or "good" hemostatic efficacy generally had higher baseline anti-fXa levels than those with "poor/none" hemostatic efficacy, with broadly comparable anti-fXa declines with ANDEXXA treatment. This finding is also not unexpected given the mechanism of action of the drug. ANDEXXA would have less of a clinical impact on subjects with lower baseline anti-fXa activity, as

such bleeds are more likely to be dependent on external factors such as the size/anatomy of the lesion and the rate of extravasation, than those with higher baseline anti-fXa levels.

- Some subjects with "poor/none" hemostatic efficacy had similar decreases in anti-fXa levels with ANDEXXA treatment. Importantly, anticoagulant reversal, while necessary for the cessation of bleeding, may not be sufficient to always produce a positive hemostatic response.

4.4. Efficacy results on datasets with a cutoff date of April 20, 2017, reviewer's analyses

<u>**Baseline characteristics and demographics**</u>

In the Safety Analysis Population of 185 subjects, most subjects were white (84.15%) and non-Hispanic (95.14%). There were 96 (51.89%) males and 89 (48.11%) females. The mean age at screening was 76.30 years (± 11.34; range 24–97 years). The distributions of these variables are similar in the Efficacy Analysis Population.

<u>**Efficacy data**</u>

- **Anti-fXa activity**

The median nadir value and decrease from baseline to nadir in anti-fXa activity observed are summarized in Table 3, for subjects in the Efficacy Analysis Population. The 95% CI provided was based on a non-parametric method. The results of enoxaparin are not presented due to the small number of subjects (n=2). Please note the total number of subjects do not add up to 108 because some subjects had missing nadir values.

Table 3. Summary of Anti-fXa Activity in Efficacy Analysis Population

	n	Nadir value median (95% CI)	Absolute change median (95% CI)	Percent change median (95% CI)
All fXa inhibitors	99	11.10 (9.50, 13.50)	-147.40 (-161.70, -127.00)	-92.27% (-93.56%, -90.26%)
apixaban	57	11.00 (8.60, 12.90)	-145.70 (-157.10, -117.70)	-92.60% (-93.84%, -91.38%)
rivaroxaban	40	13.50 (9.10, 25.30)	-165.75 (-195.80, -137.80)	-90.57% (-93.82%, -86.66%)

- **Hemostatic efficacy**

I confirmed the applicant's hemostatic efficacy results provided in Table 1. In addition, I conducted subgroup analyses by sex and age group, and did not identify any noticeable difference.

All the subjects receiving enoxaparin or edoxaban were in the higher dose regimen of ANDEXXA: 800 mg bolus + 960 mg continuous infusion. For subjects receiving rivoroxaban, they were in the smaller dose regimen (400 mg bolus + 480 mg continuous infusion) if they received rivaroxaban >7 hours ago; otherwise they received the large dose. Hemostatic success was 76.32% (29/38: 24 "excellent" and 5 "good") in the lower dose and 100% (4/4: all "excellent") in the higher dose for rivoroxaban.

- **Analysis of anti-fXa activity and hemostatic efficacy**

This is item 3 in the applicant's analyses in Section 4.3. Although there were some minor differences (e.g. number of subjects), my results (Figures 3 and 4) are consistent overall with those of the applicant (Figures 1 and 2). The differences were due to slightly different inclusion criteria for analysis, coding, *etc*.

Figure 3. Time Course of Anti-fXa Activity by Hemostatic Outcome: Apixaban
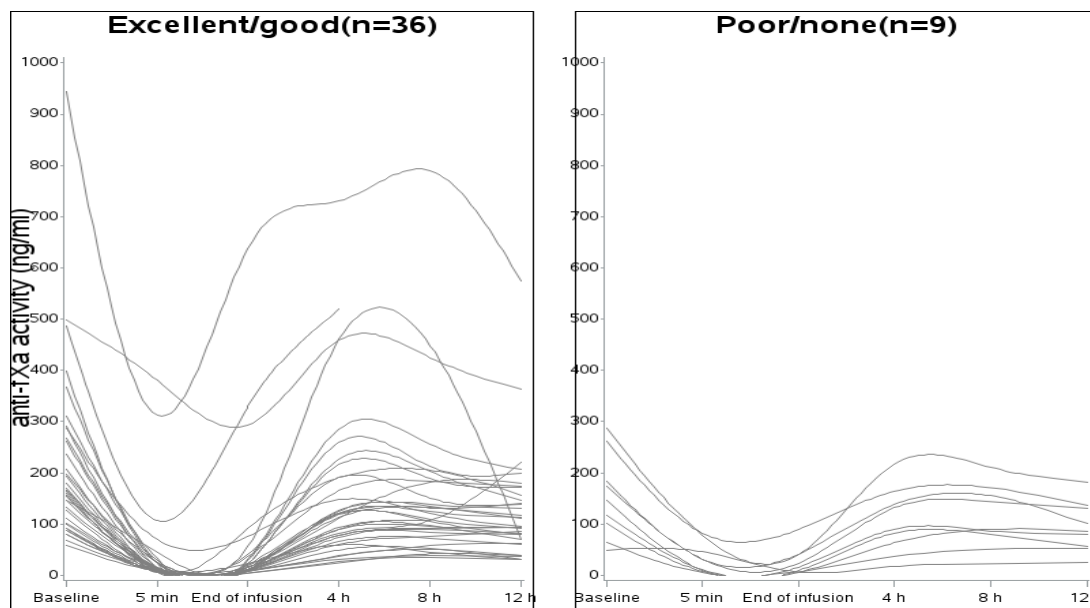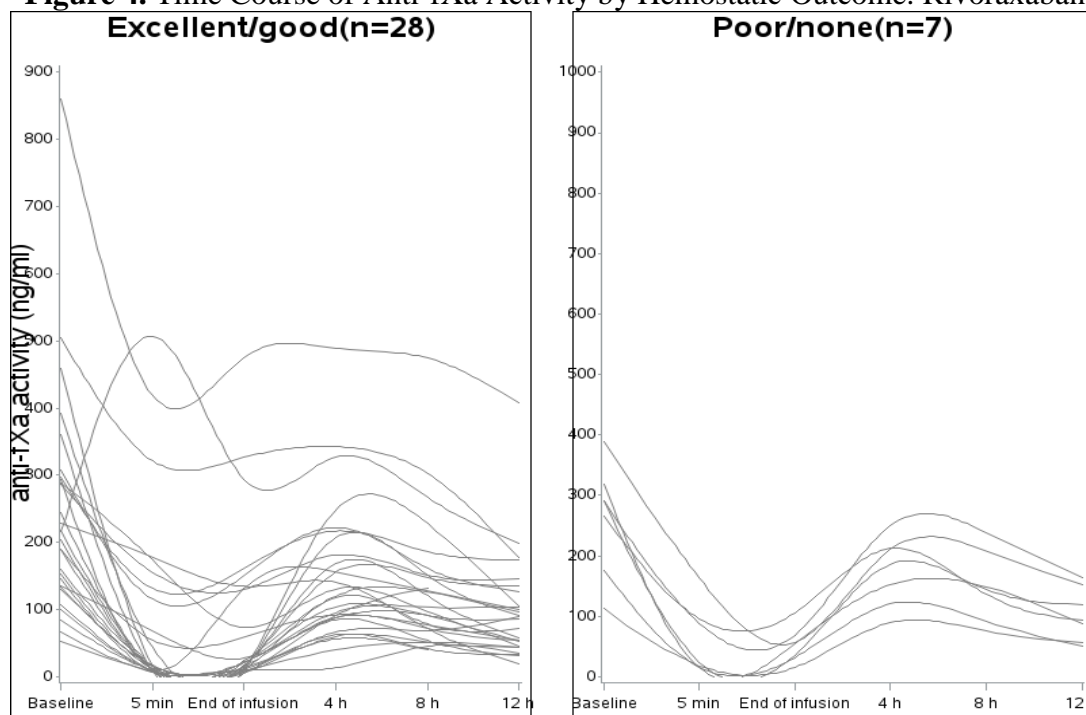

Figure 4. Time Course of Anti-fXa Activity by Hemostatic Outcome: Rivoraxaban

4.5. Safety results provided by the applicant

The following safety results were extracted from the resubmission. For more information, please refer to the clinical review memo.

Of the 185 subjects in the Safety Analysis Population, a total of 23 subjects experienced at least 1 reported TE. Of these 23 subjects, 16 have been confirmed by the independent EAC, while 7 remain pending adjudication. Seven subjects had a TE that was considered related to ANDEXXA by the investigator, of which 4 occurred within 24 hours after ANDEXXA treatment.

No subjects in the Safety Analysis Population experienced an infusion-related reaction.

Overall there were 23 deaths that occurred prior to the 30 day follow up visit in the DSUR Safety Population. Table 4 provides information on deaths by causal category and antecedent TE (if any).

Table 4. Summary of Deaths (DSUR Safety Population)

	DSUR Safety Population (N=185)
Number of Patients Dead	23 (12.4%)
All Non-cardiovascular	15 (8.1%)
Respiratory Failure	3 (1.6%)
Accident or Trauma	1 (0.5%)
Bleeding	2 (1.1%)
Infection/Sepsis	2 (1.1%)
Other Non-vascular Cause	7 (3.8%)
All Cardiovascular	8 (4.3%)
Sudden Cardiac Death (including unwitnessed)	3 (1.6%)
Cardiac Mechanical/Pump Failure	1 (0.5%)
Stroke	1 (0.5%)
Other Cardiovascular Cause	3 (1.6%)
Death Preceded by	
Myocardial Infarction	0
Stroke	2 (1.1%)
Pulmonary Embolism	1 (0.5%)
Deep Vein Thrombosis	1 (0.5%)

Source: Table 10 in 14-505 Clinical Study Report Addendum, 125586/0/76

Three deaths were associated with AEs assessed by the PI to be probably or possibly related to ANDEXXA treatment.

- Subject (b) (6) experienced an ischemic stroke on study day 1, approximately 3 hours after the end of the ANDEXXA infusion. The subject subsequently died on

study day 12 (the cause of death was indicated by the investigator to be a subdural hematoma).

- Subject (b) (6) experienced a sudden death of unknown cause on study day 15. The subject was discharged to a rehabilitation facility on study day 15, however, 3.5 hours after discharge, the subject returned to the hospital with sudden onset confusion, pallor, and unresponsiveness, and he was unable to be resuscitated. The EAC determined the cause of death to be a sudden cardiac death (including unwitnessed).

- Subject (b) (6) suffered a cardiac arrest and expired on study day 1.

Overall, 65 (35.1%) of the 185 subjects in the Safety Analaysis Population had at least 1 SAE; there were a total of 117 SAEs. Ten subjects experienced a total of 16 SAEs that were considered by the investigator to be possibly or probably related to ANDEXXA. Of these events, 8 SAEs in 5 subjects occurred within 72 hours of ANDEXXA administration.

5. Conclusions and Recommendations

1) I verified the results in two completed Phase 3 studies (14-503 and 14-504) of healthy volunteers. Both studies met their success criteria: significant greater anti-fXa activity reduction was observed in subjects in the ANDEXXA group compared to the placebo group.

2) The Phase 3b/4 study ANNEXA-4 (14-505) on acute bleeding subjects is currently ongoing. I confirmed the applicant's analyses based on data with cutoff date of April 20, 2017.

   - For hemostatic efficacy, 82.42% (75/91, 95%CI [73.02%, 89.60%]) of the subjects achieved an "excellent" or "good" outcome, and the results were overall consistent across fXa inhibitor and primary bleed type.

   - Most subjects obtained significant reduction of anti-fXa activity after the infusion of ANDEXXA.

3) The response to the only statistical item in the complete response letter is acceptable.

4) There are no outstanding statistical issues associated with this BLA.