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Applicant	Portola Pharmaceuticals Inc
Established Name	Coagulation Factor Xa (Recombinant), Inactivated
(Proposed) Trade Name	ANDEXXA
Indication(s) and Intended Population(s)	ANDEXXA is indicated for subjects treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as: <ul style="list-style-type: none"> • In life-threatening or uncontrolled bleeding • (b) (4)

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GLOSSARY

Abbreviation Definition

CI	Confidence interval
CR	Complete response
EAC	Efficacy adjudication committee
ETP	Endogenous thrombin potential
fXa	Factor Xa
GI	Gastrointestinal
ICH	Intracerebral hemorrhage
IR	Information request
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IV	Intravenous
mITT	Modified intent-to-treat
PK	Pharmacokinetic(s)
PP	Per Protocol
SAE	Serious adverse event
SD	Standard deviation
TEAE	Treatment emergent adverse event

1. EXECUTIVE SUMMARY

The applicant has developed a recombinant factor Xa (rfXa) derivative (ANDEXXA) for use as a universal antidote to direct and indirect fXa inhibitors. ANDEXXA is a modified fXa protein which has been truncated and inactivated to remove physiologic blood coagulation factor activity while retaining its high affinity for fXa inhibitors.

This application is reviewed under the Accelerated Approval pathway. In addition, it is a priority review with a review time of 8 months. It contains five completed studies (two Phase 1, one Phase 2, and two Phase 3) on healthy subjects and one ongoing Phase 3b/4 study on the diseased population. The two Phase 3 studies and the Phase 3b/4 study are covered in this review.

The primary objective of the two Phase 3 studies was to compare ANDEXXA and placebo with respect to reversal of apixaban/rivaroxaban anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion. They were randomized, double-blind, placebo-controlled, single site trials on elderly healthy volunteers. The total sample size was 68 and 80 subjects, respectively. These two studies won all the primary and secondary efficacy endpoints: significant difference of anti-fXa activity reduction was observed between subjects in the ANDEXXA and placebo groups, similarly for the free apixaban/rivaroxaban concentration, and restoration of thrombin generation. For example, for Study 14-503 (apixaban), in Part 1, the mean (SD) 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 ($p < 0.0001$), and in Study 14-504 (rivaroxaban) the Part 1 results were -92.22% (10.70%) and -17.08% (14.92%), respectively ($p < 0.0001$). The results were verified. In both studies, there was an apparent rebound of the anti-fXa activity in the ANDEXXA group. The short duration

(2-4 hours) of reversal could be concerning. I defer to the clinical team for further evaluation.

The ongoing Phase 3b/4 study is a multinational, open-label, single-arm study in subjects presenting with acute major bleeding and receiving direct or indirect fXa inhibitors. Study subjects receive ANDEXXA as an IV bolus followed by a continuous infusion for 120 minutes. The primary efficacy endpoint is the achievement of hemostatic efficacy (rated as “excellent” or “good”) of stopping an ongoing major bleed at 24 hours from the start of the ANDEXXA bolus. As of June 9, 2016, 110 subjects have been enrolled and treated in the trial. Data from 52 subjects were evaluable for hemostatic efficacy. Among them, 44(84.6%) hemostatic outcomes were either “excellent” (37) or “good” (7). Only eight subjects had “poor” outcomes. The available data from this study is not sufficient to conclude or rule out a correlation between the effects of ANDEXXA on anti-fXa activity and hemostatic outcomes.

Information request (IR) regarding some minor data inconsistencies in the two Phase 3 studies was sent on April 6, 2016. In the responses, the applicant addressed most of the issues satisfactorily except for one. One statistical comment will be included in the complete response (CR) letter. The CR letter will be issued mainly due to CMC and clinical issues.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

Direct and indirect fXa inhibitors are associated with an increase in bleeding events, some of which are life-threatening or fatal.

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

Currently there are no products approved to serve as an antidote to direct and indirect fXa inhibitors.

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

IND 15089 for ANDEXXA was submitted to the FDA on April 23, 2012. ANDEXXA was granted Breakthrough Product status on November 22, 2013, and received Orphan Drug Designation on February 23, 2015.

This original BLA submission was received on November 6, 2015, including Module 2 (nonclinical parts 2.4 and 2.6 only) and Module 4. The first amendment was received on December 17, 2015, to include the remaining modules. The PDUFA timeline started from Amendment 1. The final Clinical Study Report of Study 12-502 (edoxaban) was received on January 15, 2016 in Amendment 2, along with an updated Module 2 with Summary of Clinical Safety (2. 7.4). Day 90 and 180 updates were received on March 11, 2016, and June 14, 2016, respectively, to provide updated efficacy and safety information for the ongoing Phase 3b/4 study.

This application is reviewed under the Accelerated Approval pathway. Additionally, it is a priority review with a review time of 8 months.

ANDEXXA is orphan designated for “reversing the anticoagulant effect of direct or indirect factor Xa inhibitors in patients experiencing a serious uncontrolled bleeding event (b) (4)” and therefore does not trigger Pediatric Research Equity Act. Pediatric studies are not required.

The format and content of this submission were in accordance to the agreements made during the pre-BLA CMC meeting on October 6, 2015, and the pre-BLA Clinical-Nonclinical meeting on October 8, 2015. Based on the agreements:

- In lieu of an Integrated Summary of Efficacy (ISE), the relevant studies may be presented in adjacent tables to demonstrate the consistency of efficacy in the Phase 2 and Phase 3 studies with identical fXa inhibitors and similar ANDEXXA dosing.
- For the Phase 3b/4 study (14-505), it is acceptable to present the individual subject summaries and subject-level data listings.
- The applicant will update FDA twice (Day 90 and Day 180, respectively) on safety and efficacy data for the ongoing Study 14-505.

The originally proposed indication is for subjects treated with a direct or indirect fXa inhibitor when reversal of anticoagulation is needed in situations such as:

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

The following potential review issues were identified as indicated in the FDA’s filing letter dated February 16, 2016:

- The ongoing Phase 3b/4 trial does not appear to be "adequate and well-controlled” within the meaning of Accelerated Approval regulations and guidance.
- There does not appear to be sufficient evidence to support an indication of reversal of anticoagulation for subjects treated with the indirect FXa inhibitors.
- To support the indication for use for reversal of anticoagulation in subjects requiring reversal for (b) (4), data from an adequate and well-controlled (b) (4) study should be provided.
- Discussion and analysis of submitted interim safety and efficacy data from the 17 subjects from the ongoing Phase 3b/4 study should be provided, and similarly when submitting the 3 month safety update.

To address FDA’s above concern (Phase 3b/4 trial not being "adequate and well-controlled”) and based on FDA’s suggestion, the applicant submitted a protocol titled “Prospective Study of Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding and Receive Usual Care (ANNEXA-Usual Care)” under IND 15089 on April 19, 2016. FDA’s advice letter regarding this protocol was sent out on June 10, 2016.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

This BLA contains five completed studies on healthy subjects and one ongoing Phase 3b/4 study on the diseased population:

- Two Phase 3 studies, Study 14-503 (apixaban) and Study 14-504 (rivaroxaban),
- One Phase 2 Study 12-502 (apixaban, rivaroxaban, enoxaparin, and edoxaban),
- Two Phase 1 studies, Study 14-506 (apixaban) and Study 11-501 (ANDEXXA alone), and
- One Phase 3b/4 Study 14-505 in subjects receiving an fXa inhibitor who have acute major bleeding.
 - Amendment 1: data from 17 subjects with fully or partially adjudicated datasets were provided.
 - Amendment 11 (Day 90 update): as of March 11, 2016, 77 subjects have been enrolled and treated in the trial. Data from 35 cumulative subjects were available and included in the efficacy population.
 - Amendment 38 (Day 180 update): as of June 9, 2016, 110 subjects have been enrolled and treated in the trial. Data from 57 cumulative subjects were available and included in the efficacy population. The other 53 subjects were excluded from the analysis, mainly due to eligibility issues (e.g., baseline value for anti-fXa activity did not meet the pre-specified threshold) or the primary efficacy endpoint was pending for adjudication.

The main focus of this review is the two Phase 3 studies, to be covered in Sections 6.1 and 6.2 respectively. Study 14-505 will be briefly reviewed in Section 6.3.

Study 11-501 was the first in human study to assess the safety, tolerability, PK, and PD of ANDEXXA. It was not included in the integrated summary of safety (ISS) because it was conducted in subjects who did not receive an fXa inhibitor; thus, it does not provide direct safety support for the indication and dosing regimens.

Study 11-502 assessed the safety, tolerability, PK, and PD of ANDEXXA after dosing to steady-state with one of four direct/indirect fXa inhibitors in healthy volunteers. Study 11-506 assessed the PK of ANDEXXA in healthy subjects receiving apixaban.

Studies 11-502 and 11-506 will not be reviewed individually, but will be included in ISS.

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

The following documents submitted under BLA 125586/0/1 were reviewed.

- Module 1.2 Reviewer's Guide
- Module 1.6.3 FDA Meeting Minutes
- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 5.2 Tabular Listing of all Clinical Studies
- Module 5.3.5.1 Studies 14-503, 14-504, and 14-505

The following documents submitted under BLA 125586/0/2 were reviewed.

- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5.3 ISS

The following documents submitted under BLA 125586/0/11 were reviewed.

- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5.1 Individual study report (14-505)

The following documents submitted under BLA 125586/0/38 were reviewed.

- Module 2.5 Clinical Overview
- Module 2.7.3 Summary of Clinical Efficacy
- Module 2.7.4 Summary of Clinical Safety
- Module 5.3.5.1 Individual study report (14-505)

The following document submitted under BLA 125586/0/52 was reviewed.

- Module 1.11.3 Efficacy Information Amendment

5.3 Table of Studies/Clinical Trials

The clinical program comprised six studies, presented in Table 1.

Table 1. Overview of ANDEXXA Clinical Studies

Study number	Study design	Primary objective	Population (all healthy subjects except for 15-505)	Study status
11-501	Phase 1, randomized, double-blind, single ascending dose	Bioavailability in healthy volunteers	n=32 (24 vs. 8)*	Completed
14-506	Phase 1, open-label, two age groups	PK of ANDEXXA in younger and older healthy volunteer subjects receiving apixaban	n=10 (18-45 years); n=10 (>65 years)	Completed
12-502	Phase 2, randomized, double-blind, cohort dose escalation	PD/PK of ANDEXXA after dosing to steady state with one of four direct/indirect fXa inhibitors in healthy volunteers	Apixaban: n=54 (36 vs. 18)	Completed
			Rivaroxaban: n=45 (30 vs.15)	
			Enoxaparin: n=27 (18 vs. 9)	
			Edoxaban: n=28 (19 vs. 9)	
14-503	Phase 3, randomized, double-blind	Safety and the reversal of apixaban anticoagulation with ANDEXXA in older healthy volunteer subjects	Ages 50-75 Part 1: n=33 (24 vs.9) Part 2: n=32 (24 vs.8)	Completed
14-504	Phase 3, randomized, double-blind	Safety and the reversal of rivaroxaban anticoagulation with ANDEXXA in older healthy volunteer subjects	Ages 50-75 Part 1: n= 41 (27 vs.14) Part 2: n= 39 (26 vs.13)	Completed
15-505	Phase 3b/4, prospective, open-label, multicenter	<u>Efficacy and safety study</u> in subjects receiving a factor Xa inhibitor who have acute major bleeding	Goal: n=162 evaluable (up to 250 enrolled)	Ongoing, available data from 57 subjects submitted

*: 24 ANDEXXA, 8 placebo

Source: Original BLA 125586/0/1; Adapted from Module 5.2 Tabular listing of all clinical studies, Table 1-2, p.8

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study 14-503 (apixaban)

6.1.1 Primary Objective

The primary objective was to compare ANDEXXA and placebo with respect to reversal of apixaban anticoagulation as measured by anti-fXa activity, both after a bolus and after a bolus followed by a continuous infusion for 120 minutes.

6.1.2 Design Overview

This was a randomized, double-blind, placebo-controlled, single site trial. Study subjects were administered apixaban 5 mg orally every 12 hours for 3.5 days (to steady state), then received a bolus (Part 1) or a bolus followed by a continuous infusion (Part 2). The bolus was started 3 hours after the last apixaban dose. For each part, subjects were randomized to receive either ANDEXXA or placebo in a 3:1 ratio using permuted blocks.

Study subjects were domiciled at the study site for 8 days and were followed for safety approximately through Day 43. Day 1 was defined as the first day of apixaban administration.

6.1.3 Population

This was a volunteer population of older subjects (ages 50–75 years).

6.1.4 Study Treatments or Agents Mandated by the Protocol

ANDEXXA was administered IV as a bolus of 400 mg at a target rate of approximately 30 mg/minute for 13 minutes (Part 1), or as a bolus (same dose and rate) followed by a continuous infusion of 480 mg at 4 mg/minute for 120 minutes (Part 2).

6.1.8 Endpoints and Criteria for Study Success

Reversal of anticoagulation was evaluated by measuring anti-fXa activity (primary efficacy measure), unbound apixaban plasma levels, and thrombin generation (secondary efficacy measures). The primary endpoint was percent change from baseline in anti-fXa activity at the nadir where nadir was defined as:

- the smaller value for anti-fXa activity at the +2 minute or +5 minute time point following the end of the bolus in Part 1,
- the smallest value for anti-fXa activity among the 110-minute (10 minutes prior to the end of the continuous infusion), the 2-minute, and 5+minute time points after the end of the continuous infusion in Part 2.

The baseline for the primary endpoint in both parts was the anti-fXa activity just prior to administration of ANDEXXA/placebo, 3 hours following the Day 4 dose of apixaban. All hypothesis tests were two-sided and performed at the 0.05 significance level.

Secondary efficacy endpoints for Part 1 include

- 1) The occurrence of $\geq 80\%$ reduction in anti-fXa activity from its baseline to nadir, where nadir is defined as the smallest value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the ANDEXXA bolus.
- 2) The change from baseline in free apixaban concentration (ng/ml) at nadir, where nadir is defined as the smallest value for free apixaban concentration at the +2 minute or +5 minute time point after the completion of the ANDEXXA bolus.
- 3) The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the +2 minute time point and the +10 minute time point after the end of the ANDEXXA bolus (inclusive).

- 4) The occurrence of thrombin generation above the lower limit of the normal range at its peak, between the +2 minute time point and the +10 minute time point after the end of the ANDEXXA bolus (inclusive).

Secondary efficacy endpoints for Part 2 include

- 1) The percent change from baseline in anti-fXa activity at its nadir, where nadir is defined as the smallest value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the ANDEXXA bolus.
- 2) The occurrence of $\geq 80\%$ reduction in anti-fXa activity from its baseline to nadir, where nadir is defined as the smallest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- 3) The change from baseline in free apixaban concentration (ng/ml) at its nadir, where nadir is defined as the smallest value for free apixaban between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- 4) The change in thrombin generation from baseline to its peak, where peak is defined as the largest value for thrombin generation between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).
- 5) The occurrence of thrombin generation above the lower limit of the normal range at its peak, where peak is defined as the largest value for anti-fXa activity between the 110-minute time point (10 minutes prior to the end of the continuous infusion) and the 5-minute time point after the end of the continuous infusion (inclusive).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample size justification

The sample size calculations assumed the same efficacy as observed in the Phase 2 study (Study 12-502). For Part 1, the mean (SD) percent changes in anti-fXa activity from its nadir to baseline at 2 minutes were -95.0% (1.4%) vs. 11.4% (15.9%) for ANDEXXA and placebo, respectively. For Part 2, the mean (SD) percent changes in anti-fXa activity from its nadir to baseline at 120 minutes were -91.3% (2.3%) vs. -33.4% (11.6%) for ANDEXXA and placebo, respectively. With these assumptions, a total of 32 subjects randomized in a 3:1 ratio (ANDEXXA : placebo) should sufficiently power (>99% power) both Part 1 and Part 2.

Definition of analysis populations

- Safety analysis population: all subjects randomized and treated with any amount of study drug.
- Primary efficacy analysis population (modified intent-to-treat [mITT]):

- Part 1: all randomized subjects who received any amount of study drug treatment and had baseline value for anti-fXa and at least one of the following time points: +2 minute or +5 minute time point after the end of the bolus.
- Part 2, all randomized subjects who received any amount of study drug treatment and had baseline for anti-fXa and at least one of the following time points: 110-minute time point during the continuous infusion, -2 minute time point during the continuous infusion, or +5 minute time point after the end of the continuous infusion.
- Per-Protocol (PP) population: all mITT subjects who received the full dose of medication administered as prescribed. All subjects in the PP population were analyzed based on the actual treatment received.

Analysis of primary efficacy endpoint

The comparison was conducted using an exact Wilcoxon rank-sum test.

Sensitivity analyses

For the endpoints that were defined as percent change from baseline, missing data was imputed with 0.0% (i.e., using the baseline value as the nadir value). For the dichotomous endpoints, a missing outcome was considered a treatment failure.

Analysis of secondary efficacy endpoints

The dichotomous secondary endpoints were compared between treatment groups using Fisher's Exact Test. The secondary endpoints which were defined as change from baseline (continuous measure) between treatment groups were compared using an exact Wilcoxon rank-sum test.

A sequentially closed testing procedure as a gate-keeping method was used to compare the secondary endpoints after the primary endpoint comparison was rejected in favor of the treatment group. The order of hypothesis follows the order of the secondary endpoints specified in Section 6.1.8.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

A total of 68 unique subjects received apixaban (34 in Part 1 and 34 in Part 2). Of these, 66 subjects were randomized (34 subjects in Part 1 [25 ANDEXXA, 9 placebo] and 32 in Part 2 [24 ANDEXXA, 8 placebo]). Analysis populations and disposition of subjects is presented in Table 2.

Table 2. Analysis Populations and Final Study Disposition, 14-503

Characteristic Category	Part 1			Part 2		
	Andexanet N=25 n (%)	Placebo N=9 n (%)	Total N=34 n (%)	Andexanet N=24 n (%)	Placebo N=8 n (%)	Total N=32 n (%)
Subjects who Received Apixaban (i.e., “enrolled”)	NA	NA	34	NA	NA	34
Subjects Randomized	25	9	34	24	8	32
Safety Analysis Population ^a	24 (96.0)	9 (100.0)	33 (97.1)	24 (100.0)	8 (100.0)	32 (100.0)
Efficacy Analysis Population (mITT) ^a	24 (96.0)	9 (100.0)	33 (97.1)	23 (95.8)	8 (100.0)	31 (96.9)
Per-protocol Population ^a	24 (96.0)	9 (100.0)	33 (97.1)	23 (95.8)	8 (100.0)	31 (96.9)
Completed the Study ^b	24 (96.0)	9 (100.0)	33 (97.1)	24 (100.0)	8 (100.0)	32 (100.0)

Source: Original BLA 125586/0/52; Study Report 14-503, updated Table 5 and Table 7

In Part 1, one subject ((b) (6)) randomized to the ANDEXXA group did not receive study drug due to an IV access issue, and thus was excluded from the Safety, mITT, and PP populations. The subjects in the Safety and Efficacy Analysis (mITT) populations were identical.

In Part 2, all subjects were included in the safety analysis and completed the study. One subject ((b) (6)) randomized to the ANDEXXA group was not included in the Efficacy Analysis (mITT) or PP Populations because study drug was discontinued partway through the infusion due to an AE (mild hives) and the site did not collect follow-up blood tests on that day, as required for inclusion in the mITT Population. The subjects in the mITT and PP Populations were identical.

6.1.10.1.1 Demographics

Demographic and baseline characteristics were generally similar for subjects in the ANDEXXA and placebo groups, and similar between Part 1 and Part 2. Subjects were predominately male (58% in Part 1, 69% in Part 2), white (100% in Part 1, 91% in Part 2), non-Hispanic or non-Latino (58% in Part 1, 59% in Part 2), and had a mean age of 60 (range 50 to 73 years) in both Part 1 and Part 2.

Note: The proportion of Hispanic or Latino subjects is higher than that of the general population: Hispanics constituted 17% of the nation's total population based on 2014 census data.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The use of concomitant medications was low and similar in the ANDEXXA and the placebo groups.

6.1.10.1.3 Subject Disposition

See Section 6.1.10.1.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint

Anti-fXa levels decreased more in subjects who received ANDEXXA than in subjects who received placebo ($p < 0.0001$) in both Part 1 and Part 2. The percent change from baseline in anti-fXa activity at the nadir is presented in Table 3.

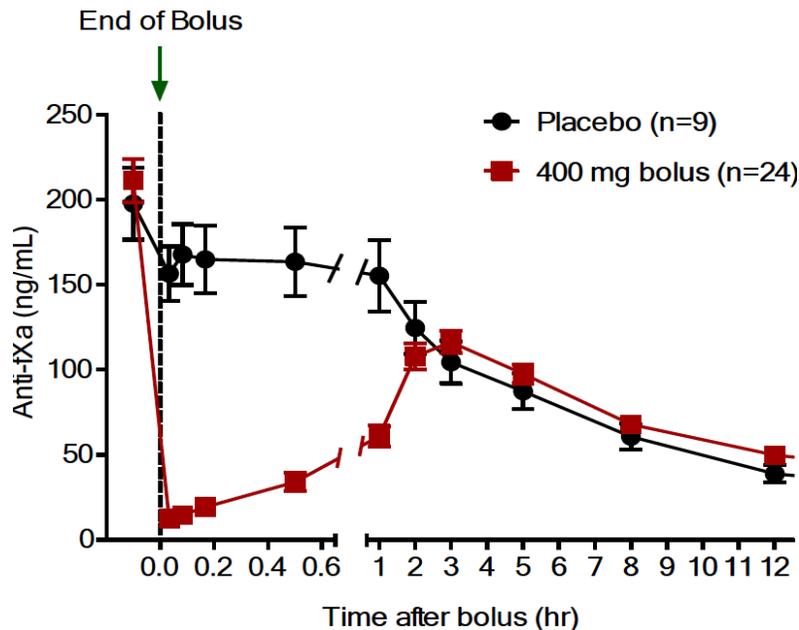
Table 3. Primary Efficacy Endpoint (mITT Population), 14-503

Percent Change from Baseline at the Nadir ^a	Part 1 (n=33)		Part 2 (n=31)	
	Andexanet n=24	Placebo n=9	Andexanet n=23	Placebo n=8
Mean (\pm SD)	-93.86 (1.650)	-20.71 (8.559)	-92.34 (2.809)	-32.70 (5.578)
Median (range)	-94.43 (-96.3, -89.7)	-18.95 (-31.6, -9.3)	-92.73 (-96.3, -83.4)	-33.01 (-40.1, -24.1)
Hodges-Lehman estimate of shift (95% CI)	-74.55 (-78.39, -66.28)		-59.50 (-64.10, -55.17)	
p-value	< 0.0001 ^b		< 0.0001 ^b	

Source: Original BLA 125586/0/52; Study Report 14-503, updated Table 5 and Table 7

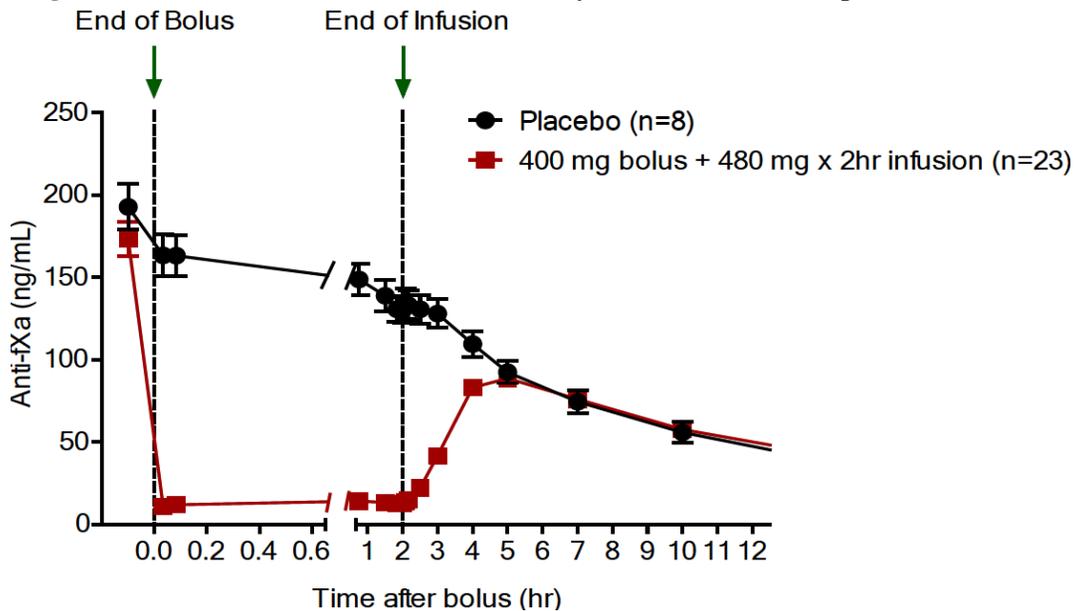
The time course of anti-fXa activity before and after administration of ANDEXXA is presented in Figure 1 (Part 1) and Figure 2 (Part 2). In both figures, after a sharp decrease, there was an apparent rebound of the anti-fXa activity in the ANDEXXA group. The curves from the two groups became very close around 2 and 4 hours after the bolus, for Part 1 and Part 2 respectively.

Figure 1. Time Course of Anti-FXa Activity —Part 1 (mITT Population), 14-503



Source: Original BLA 125586/0; Study Report 14-503, Figure 5, p.68

Figure 2. Time Course of Anti-FXa Activity —Part 2 (mITT Population), 14-503



Source: Original BLA 125586/0; Study Report 14-503, Figure 6, p.70

Sensitivity analysis: There was no missing data for Part 1. For the only subject who was excluded from mITT due to an IV access issue, the study result was robust even if 0% reduction was imputed for this subject. The only missing data in Part 2 from the ANDEXXA group was imputed by 0% reduction. The study result was robust to missing data imputation.

6.1.11.2 Secondary efficacy endpoints

1. Percent change from baseline in anti-fXa activity at the nadir (Part 2 only)

The mean percent change from baseline in anti-fXa activity at the nadir was -93.49% ($\pm 1.525\%$) for the ANDEXXA group and -16.73% ($\pm 4.104\%$) for the placebo group ($p < 0.0001$).

Note: the definition of nadir or peak for each secondary variable is provided in Section 6.1.8.

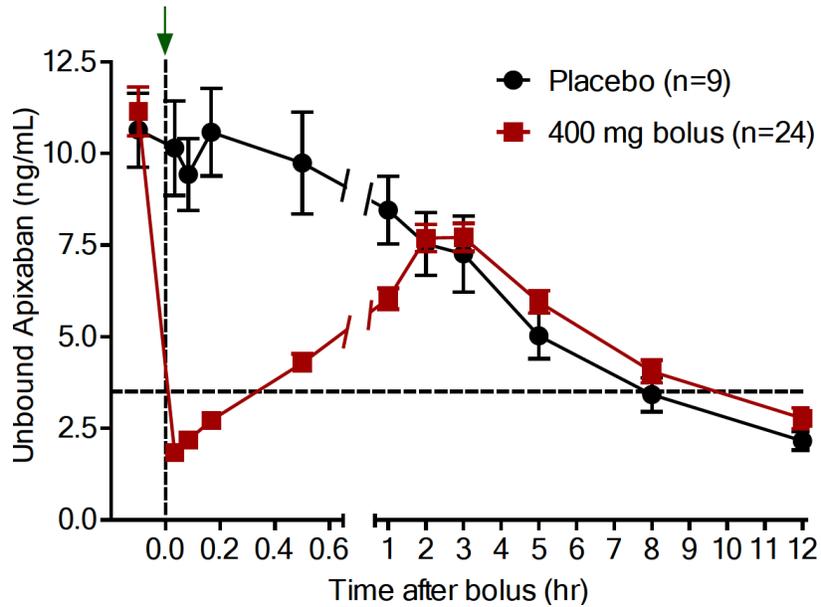
2. Occurrence of $\geq 80\%$ reduction in anti-fXa activity from its baseline to nadir

The occurrence of $\geq 80\%$ reduction in anti-fXa activity from baseline was met in 100% of subjects in the ANDEXXA group and no subjects in the placebo group ($p < 0.0001$) in both Part 1 and Part 2.

3. Change from baseline in free apixaban concentration at nadir

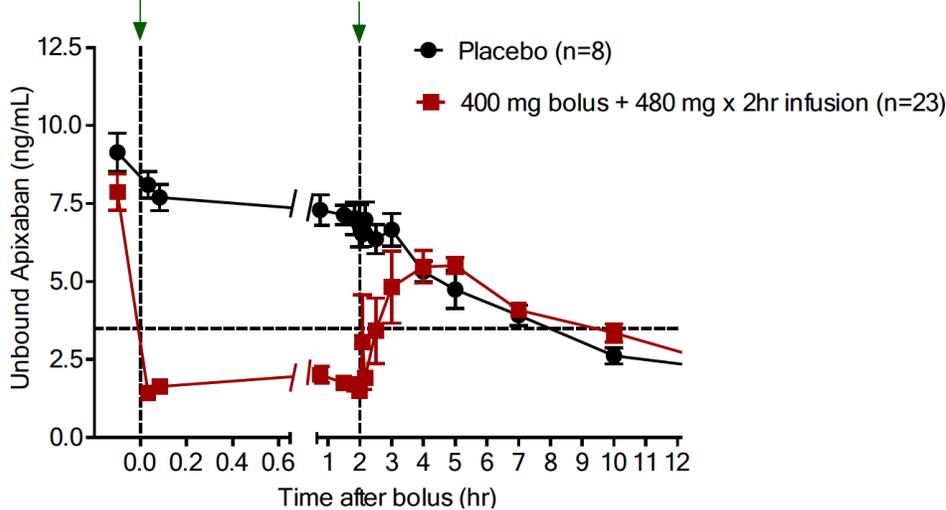
The time course of plasma concentrations of unbound apixaban before and after administration of ANDEXXA is presented in Figure 3 (Part 1) and Figure 4 (Part 2). Consistent with the time course of anti-fXa activity presented in Figures 1 and 2, the plasma concentrations of unbound apixaban had an apparent rebound after a sharp decrease.

Figure 3. Time Course of Apixaban Concentration-Part 1, 14-503
End of bolus



Source: Original BLA 125586/0; Study Report 41-503, Figure 7, p.73

Figure 4. Time Course of Apixaban Concentration-Part 2, 14-503
End of Bolus End of Infusion



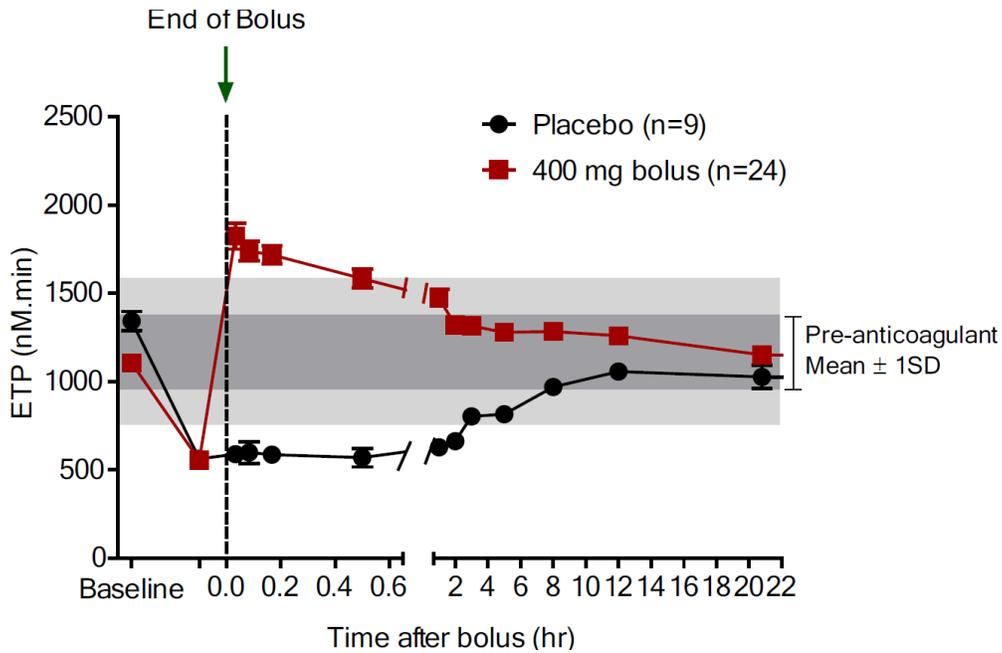
BLA 125586/0; Study Report 41-503, Figure 8, p.74

Source: Original

4. Change in thrombin generation from baseline to its peak

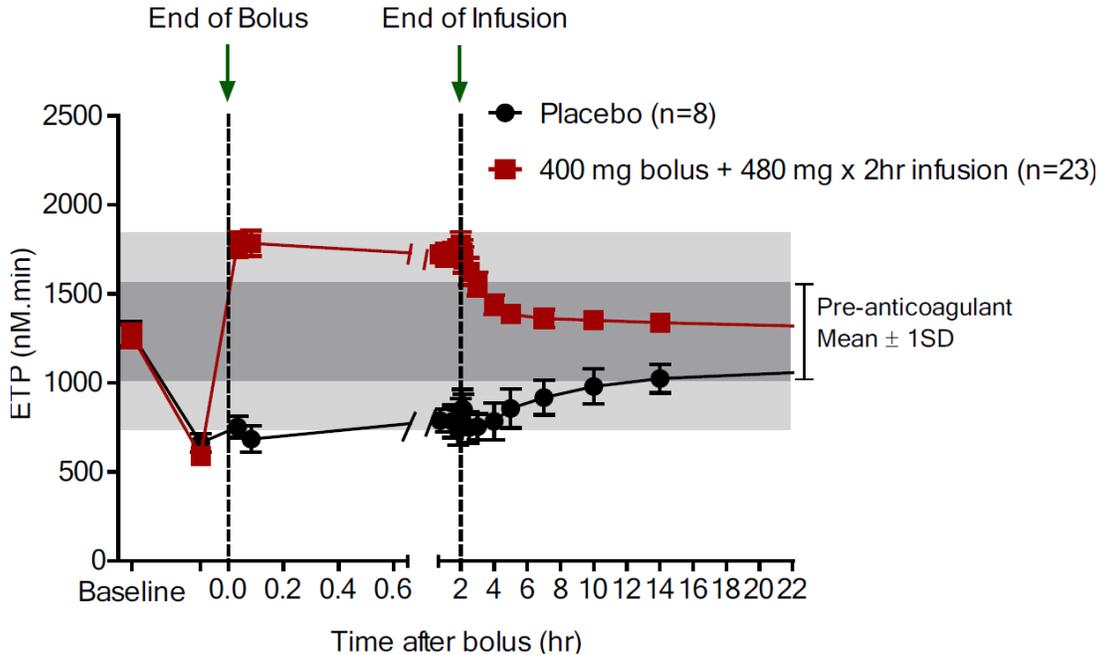
The time courses of thrombin generation before and after the administration of ANDEXXA are presented in Figure 5 (Part 1) and Figure 6 (Part 2). For both parts, the peak of the thrombin generation was reached quickly around the end of the bolus. Compared to anti-fXa activity and apixaban concentration, the separation between the ANDEXXA and placebo curves sustained longer. ETP in Figure 5 stands for endogenous thrombin potential.

Figure 5. Time Course of Thrombin Generation-Part 1, 14-503



Source: Original BLA 125586/0; Study Report 41-503, Figure 9, p.76

Figure 6. Time Course of Thrombin Generation-Part 2, 14-503



Source: Original BLA 125586/0; Study Report 41-503, Figure 11, p.78

5. Occurrence of thrombin generation above the lower limit of the derived normal range at its peak

Thrombin generation above the lower limit of the derived normal range at its peak was met by 100% of subjects in the ANDEXXA group in both Part 1 and Part 2, compared to 11% of subjects in the placebo group in Part 1 and 25% in Part 2.

6.1.11.3 Subpopulation Analyses

For both Part 1 and Part 2, subgroup analysis by age or race was not feasible for this older and white population (see Section 6.1.10.1.1). A very similar distribution was observed for the primary efficacy endpoint among the male/female and Hispanic/non-Hispanic subgroups, respectively.

6.1.11.4 Dropouts and/or Discontinuations

See the sensitivity analysis under Section 6.1.11.1.

6.1.12 Safety Analyses

There were no deaths, SAEs, thrombotic events, severe AEs, or AEs resulting in withdrawal from the study.

6.2 Study 14-504 (rivaroxaban)

This study compared the reversal of anticoagulation between ANDEXXA and placebo for another direct fXa inhibitor, rivaroxaban. The design, population, endpoints, and analysis methods of this study were very similar to those of Study 14-503. It consisted of two parts as well: bolus only (Part 1) and bolus followed by a continuous infusion (Part 2). The major difference between the two studies is the ANDEXXA dose: 400 mg bolus followed by a 120-minute, 480-mg continuous infusion for Study 14-503 and 800 mg bolus followed by a 120-minute, 960-mg continuous infusion for Study 14-504 respectively. Another difference is that the randomization ratio was 2:1 in Study 14-504, rather than 3: 1 in Study 14-503. Only the study results will be presented in this review.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

A total of 80 subjects received rivaroxaban and, therefore, were considered “enrolled.” Of these, all 80 subjects were randomized. Disposition of subjects is presented in Table 4.

Table 4. Subject Accounting and Final Study Disposition, 14-504

Characteristic Category	Part 1			Part 2		
	Andexanet N=27 n (%)	Placebo N=14 n (%)	Total N=41 n (%)	Andexanet N=26 n (%)	Placebo N=13 n (%)	Total N=39 n (%)
Subjects Who Received Rivaroxaban (ie, Enrolled)	NA	NA	41	NA	NA	39
Subjects Randomized	27 (65.9)	14 (34.1)	41 (100)	26 (66.7)	13 (33.3)	39 (100)
Safety Analysis Population	27 (100)	14 (100)	41 (100)	26 (100)	13 (100)	39 (100)
Efficacy Analysis Population (mITT)	27 (100)	14 (100)	41 (100)	26 (100)	13 (100)	39 (100)
Completed the Study	27 (100)	14 (100)	41 (100)	24 (92.3)	13 (100)	37 (94.9)

Source: Original BLA 125586/0/1; Study Report 14-504, Table 9, p.61

In Part 2, two subjects, both in the ANDEXXA treatment group, did not complete the study, but they were all included in the Efficacy and Safety analysis sets.

6.2.10.1.1 Demographics

Demographic and baseline characteristics were generally similar for subjects in the ANDEXXA and placebo groups, and similar between Part 1 and Part 2. Subjects were predominately white (78% in Part 1, 72% in Part 2), non-Hispanic or non-Latino (68% in Part 1, 64% in Part 2), male (63% in Part 1, 56% in Part 2), and had a mean age of 55 (range 50 to 65 years) in Part 1 and 57 (range 50 to 68 years) in Part 2.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The use of concomitant medications was low and similar in the ANDEXXA and the placebo groups.

6.2.10.1.3 Subject Disposition

See Section 6.2.10.1.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint

Anti-fXa levels decreased more in subjects who received ANDEXXA than in subjects who received placebo ($p < 0.0001$) in both Part 1 and Part 2. The percent change from baseline in anti-fXa activity at the nadir is presented in Table 5.

Table 5. Primary Efficacy Endpoint (mITT Population), 14-504

Percent Change from Baseline at the Nadir ^a	Part 1 (n=41)		Part 2 (n=39)	
	Andexanet n=27	Placebo n=13	Andexanet n=26	Placebo n=13
Mean (SD)	-92.22 (10.697)	-18.39 (14.662)	-96.72 (1.838)	-44.75 (11.749)
Median (range)	-94.28 (-97.0, -39.4)	-24.43 (-36.7, 12.3)	-96.62 (-100.0, -91.0)	-45.46 (-68.3, -27.8)
Hodges-Lehman Estimate of Shift (95% CI)	-70.14 (-85.43, -65.91)		-51.87 (-57.95, -47.03)	
P-value	< 0.0001 ^b		< 0.0001 ^b	

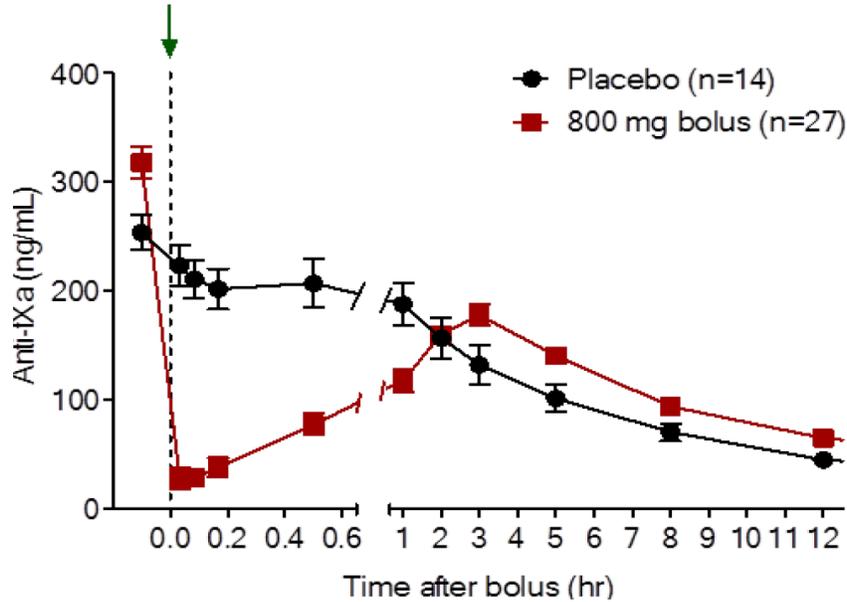
Source: Original BLA 125586/0/52; Study Report 14-504 Part 1, updated Table 11, p.67

Reviewer's comment: Above Table 11 in original submission demonstrated that there were 14 subjects in the placebo group, Part 1. However, based on this reviewer's analysis, only 13 subjects were included in the calculation. A question was raised in the IR letter. The applicant acknowledged this error and made a correction to this table to reflect only 13 subjects was included. However, all 14 subjects should be included in the primary analysis by imputing the percent change with 0% for missing value as the mITT included 14 subjects. In addition, this reviewer had another IR regarding whether the mITT should include 13 or 14 subjects, while the applicant confirmed that the mITT included 14 subjects. This was due to subject (b) (6) who had missing measurement from 2 and 5 minutes post bolus for this endpoint. Please see the sensitivity analysis with all 14 subjects included. Please note that this subject was included in Figure 7 below because he had measurements thereafter. A comment will be included in the CR letter to request for including subject (b) (6) in the primary analysis.

The time course of anti-fXa activity before and after administration of ANDEXXA is presented in Figure 7 (Part 1) and Figure 8 (Part 2). In both figures, after a sharp decrease, there was an apparent rebound of the anti-fXa activity in the ANDEXXA

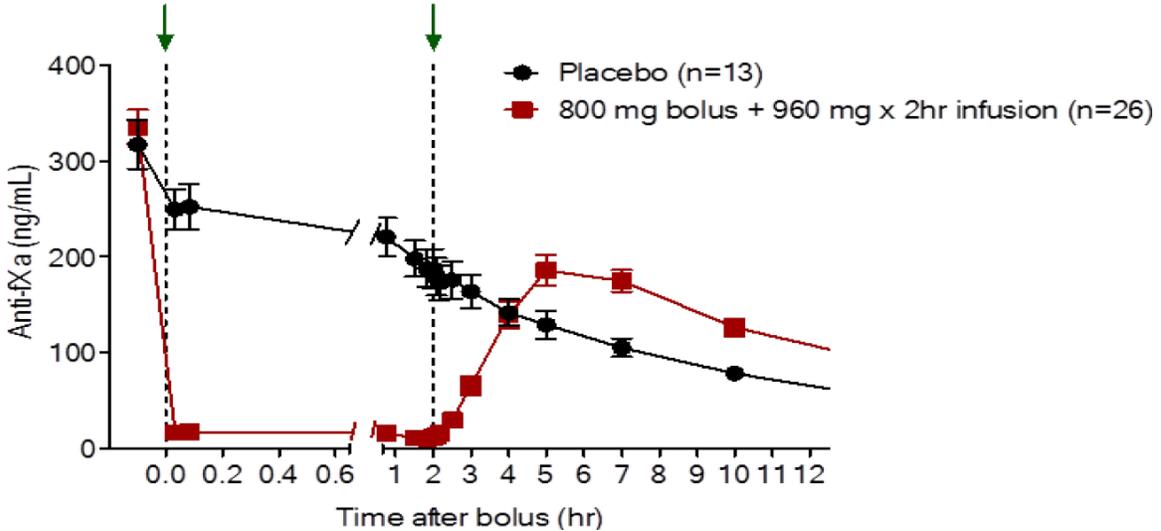
group. After crossing around 2 and 4 hours after bolus for Part 1 and Part 2 respectively, the curve of the ANDEXXA group was even higher than the curve of placebo group.

Figure 7. Time Course of Anti-FXa Activity —Part 1, 14-504
End of Bolus



Source: Original BLA 125586/0; Study Report 14-504, Figure 5 (A), p.69

Figure 8. Time Course of Anti-FXa Activity —Part 2, 14-504
End of Bolus End of Infusion



Source: Original BLA 125586/0; Study Report 14-504, Figure 6 (A), p.72

Sensitivity analysis: There was no missing data for Part 2. The only missing data in Part 1 from the treatment group (Subject (b) (6)) was imputed by 0% reduction in the primary analysis (see Table 5). However, Table 5 did not include the missing value for subject (b) (6) in the placebo group. With Subject (b) (6) from the placebo group included by imputation (0% reduction), the mean percent change from baseline (SD) changed from -18.39% (14.66%) to -17.08%(14.92%).

6.2.11.2 Secondary efficacy endpoints

1. Percent change from baseline in anti-fXa activity at the Nadir (Part 2 only)

The mean (\pm SD) percent change from baseline in anti-fXa activity at the nadir was -96.72% (\pm 1.838%) for the ANDEXXA group and -44.75% (\pm 11.749%) for the placebo group ($p < 0.0001$).

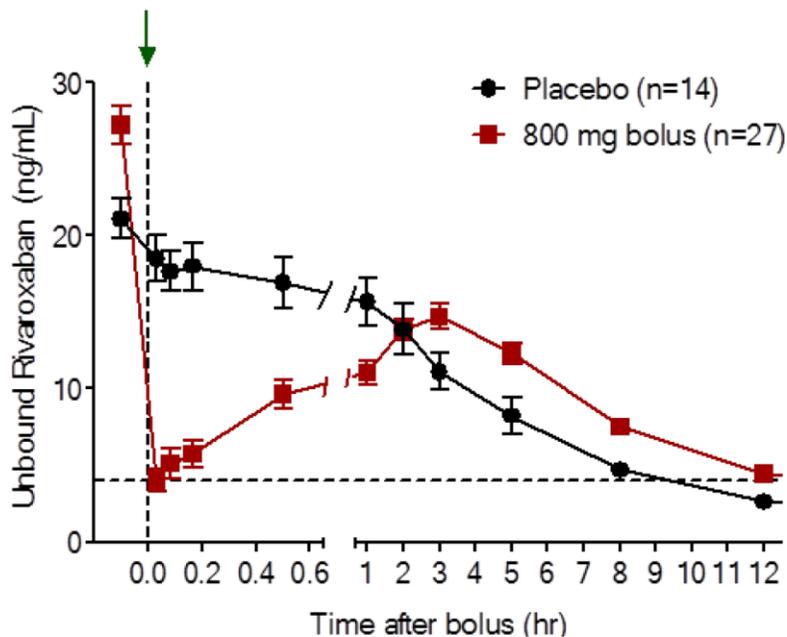
2. Occurrence of $\geq 80\%$ reduction in anti-fXa activity from its baseline to nadir

The occurrence of $\geq 80\%$ reduction in anti-fXa activity from baseline was met in 96.3% of subjects in the ANDEXXA group in Part 1 and 100% in Part 2, and no subjects in the placebo group in both Part 1 and Part 2.

3. Change from baseline in free rivaroxaban concentration at nadir

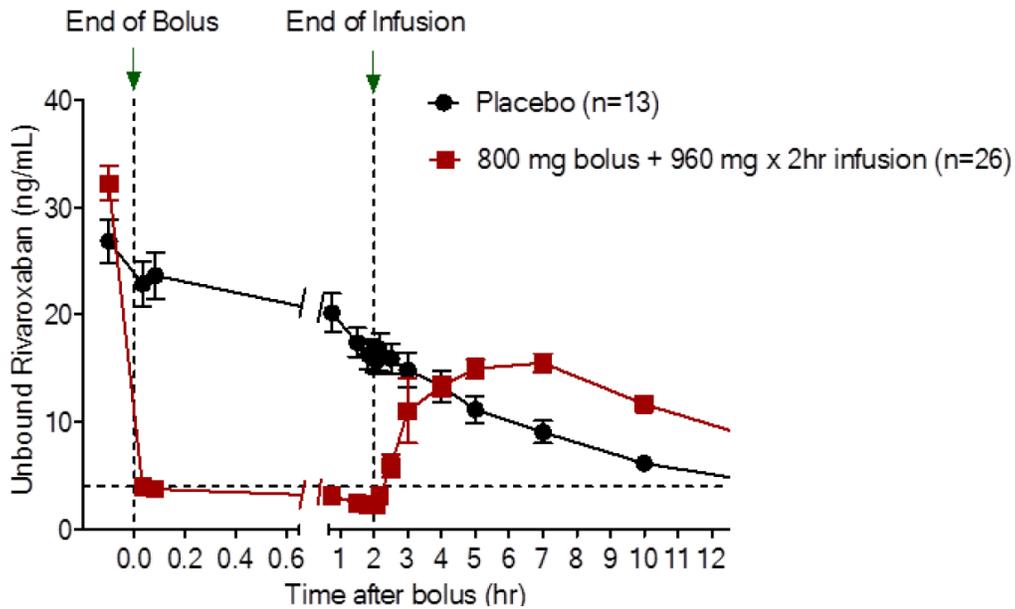
The time course of plasma concentrations of unbound rivaroxaban before and after administration of ANDEXXA is presented in Figure 9 (Part 1) and Figure 10 (Part 2). Consistent with the time course of anti-fXa activity presented in Figures 7 and 8, the plasma concentrations of unbound rivaroxaban had an apparent rebound after a sharp decrease, and the level was even higher than the placebo group level.

Figure 9. Time Course of Rivaroxaban Concentration-Part 1, 14-504
End of Bolus



Source: Original BLA 125586/0; Study Report 14-504, Figure 7, p.75

Figure 10. Time Course of Rivaroxaban Concentration-Part 2, 14-504

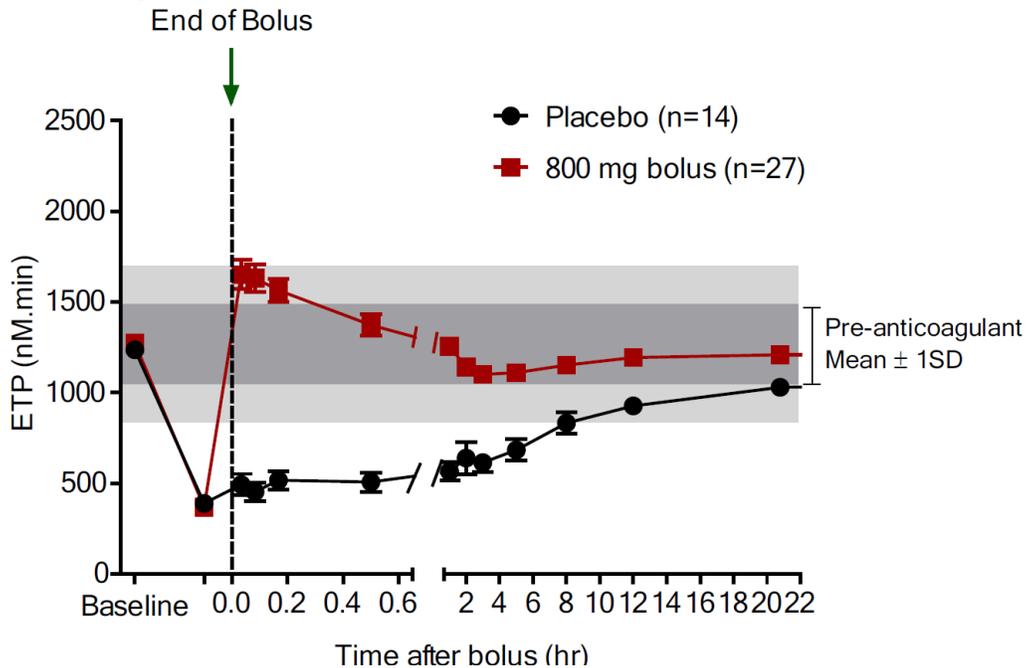


Source: Original BLA 125586/0; Study Report 14-504, Figure 8, p.76

4. Change in thrombin generation from baseline to its peak

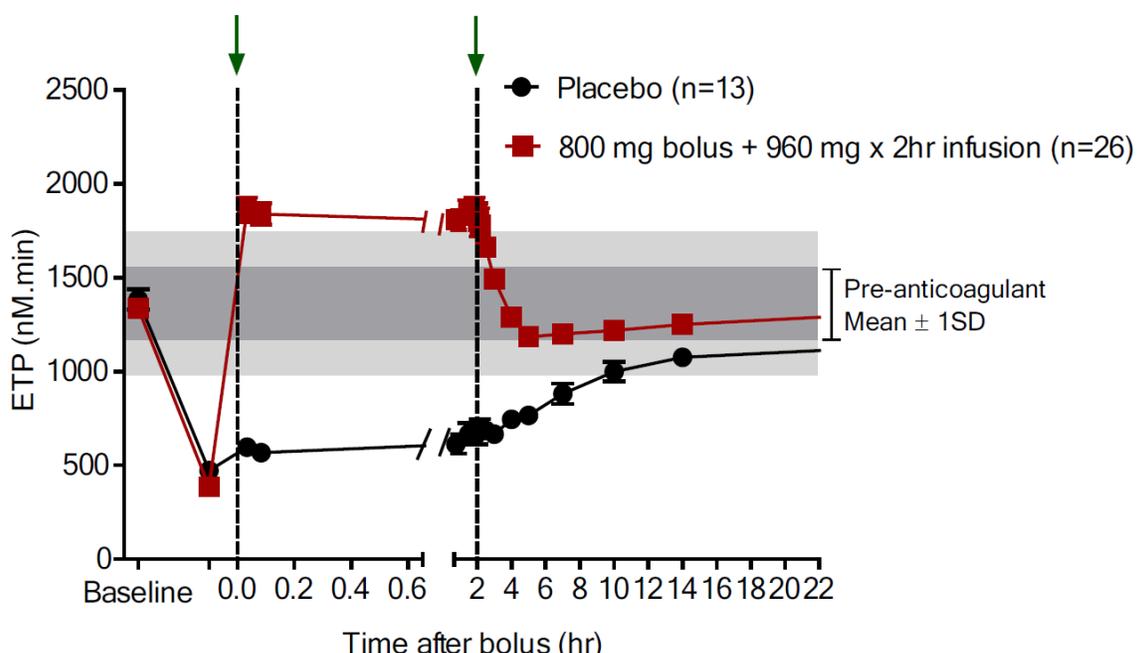
The time courses of thrombin generation before and after the administration of ANDEXXA are presented in Figure 11 (Part 1) and Figure 12 (Part 2). For both parts, the peak of the thrombin generation was reached quickly around the end of the bolus in the ANDEXXA group. Compared to anti-fXa activity and rivaroxaban concentration, the separation between the ANDEXXA and placebo curves sustained longer.

Figure 11. Time Course of Thrombin Generation-Part 1, 14-504



Source: Original BLA 125586/0; Study Report 14-504, Figure 9, p.78

Figure 12. Time Course of Thrombin Generation-Part 2, 14-504
 End of Bolus End of Infusion



Source: Original BLA 125586/0; Study Report 14-504, Figure 11, p.80

5. Occurrence of thrombin generation above the lower limit of the derived normal range at its peak

Thrombin generation above the lower limit of the derived normal range at its peak was met by 96.3% of subjects in the ANDEXXA group in Part 1 and 100% of subjects in Part 2, compared to 7.1% of subjects in the placebo group in Part 1 and 0% in Part 2.

Reviewer's comment: In Part 1, one subject ((b) (6)) from the ANDEXXA group seemed to be an "outlier" on efficacy endpoints (see Table 6). This is a 54 year old female African American. In Amendment 52, the applicant explained that this subject was confirmed to have no detectable ANDEXXA concentrations at 2 minutes and at 10 minutes post-bolus, due to a leakage of study drug from the infusion port. As a post-hoc sensitivity analysis, excluding this subject would make the results slightly better. For example, for the primary efficacy endpoint, the mean percent change of anti-fXa activity changed from -92.22% (10.70) to -94.25% (1.78). The major change was the reduction of standard deviation.

Table 6. Efficacy Endpoints of Subject (b) (6) Compared to Other Subjects

	Subject (b) (6)			Excluding Subject (b) (6) (range)		
	Baseline	Nadir/Peak	Change	Baseline	Nadir/Peak	Change
Anti-fXa activity (ng/mL)	381	231	-39%	[175, 454]	[6, 33]	[-90%, -97%]
Free rivoraxaban (ng/mL)	31	21	-32%	[12, 40]	[1, 8]	[-79%, -95%]
Thrombin generation (nM.min)	201	545	172%	[191, 628]	[1330, 2597]	[184%, 669%]

6.2.11.3 Subpopulation Analyses

Due to the enrollment restriction, subgroup analysis by age was not feasible. A very similar distribution was observed for the primary efficacy endpoint among the race, sex, and ethnicity (Hispanic/non-Hispanic) subgroups, respectively.

6.2.11.4 Dropouts and/or Discontinuations

See the sensitivity analysis under Section 6.2.11.1.

6.2.12 Safety Analyses

There were no deaths, SAEs, thrombotic events, severe AEs, or AEs resulting in discontinuing study drug administration or withdrawal from the study

6.3 Study 14-505

6.3.1 Study Design and Statistical Analysis Plan

This ongoing study was designed to meet the post-marketing requirements for Accelerated Approval: to demonstrate a correlation between the effects of ANDEXXA on anti-fXa activity and hemostatic outcomes. It is a multinational, open-label, single-arm, Phase 3b/4 study in subjects presenting with acute major bleeding and receiving direct or indirect fXa inhibitors. Acute major bleeding is objectively defined in the protocol and is not repeated here. The efficacy evaluable subjects must have a baseline value for anti-fXa activity >75 ng/mL. Up to 250 subjects may have to be treated to achieve the goal of 162 evaluable subjects, because ~30% of the safety population will have anti-fXa activity <75 ng/mL and therefore not be included in the Efficacy Analysis Population. The percentage of enrolled subjects receiving indirect fXa inhibitors will be restricted to 20%. Study subjects receive ANDEXXA as an IV bolus administered over approximately 15 to 30 minutes, followed immediately by a continuous infusion administered over approximately 120 minutes. Subjects receive one of two dosing regimens of ANDEXXA based on which fXa inhibitor they received and the dose and timing of the most recent inhibitor dose.

fXa Inhibitor	IV Bolus	IV Infusion
All patients receiving apixaban and those patients who received rivaroxaban >7 hours ago	400 mg at a target rate of 30 mg/min	480 mg @ 4 mg/min for 120 minutes
Patients who received enoxaparin, edoxaban, or a dose of rivaroxaban within ≤ 7 hours or at an unknown time*	800 mg at a target rate of 30 mg/min	960 mg @ 8 mg/min for 120 minutes

The primary efficacy endpoint is the achievement of hemostatic efficacy of stopping an ongoing major bleed at 24 hours from the start of the ANDEXXA bolus, rated by the independent Efficacy Adjudication Committee (EAC) as “excellent” or “good”. Assuming a response rate of 61%, 162 efficacy evaluable subjects will be enrolled to provide 80% power for a two-sided 95% exact CI that is completely above 50% for the primary efficacy variable.

6.3.2 Results

The results summarized below are based on the Day 180 update (Amendment 38). The results from the original submission and the Day 90 update were reviewed but are not presented here.

As of June 9, 2016, 110 subjects have been enrolled and treated in the trial. Data from 57 subjects were available and included in the efficacy population, with 54 assessed by the EAC as having a major bleed at study entry. Two subjects were assessed as “not major bleeds”, and thus were not considered evaluable for hemostatic efficacy, and one assessment was pending by the EAC. Regarding the bleeding type among these 52 subjects, 24 were gastrointestinal (GI) and urinary bleeding, 22 were intracerebral hemorrhage (ICH) bleeding, 1 was muscular/skeletal bleeding, and 5 were other bleeding. The efficacy data are summarized in Table 7, based on my analysis. Eight subjects were rated as “poor”.

Table 7. Summary of 14-505 Efficacy Data: Day 180 Update

fXa Inhibitor	# of subjects	Adjudicated hemostatic efficacy		
		Excellent	Good	Poor
Apixaban	23	16	3	4
Rivaroxaban	23	16	3	4
Enoxaban	6	5	1	
Total	52	37 (71.1%)	7 (13.5%)	8 (15.4%)

Regarding the time course profiles of anti-fXa activity in the 52 subjects with available results before and after ANDEXXA treatment, the profiles of the eight subjects with “poor” hemostatic outcome did not differentiate from the other subjects. See the figures in Appendix A for the time course of anti-fXa activity.

Reviewer’s comment: Because most of the subjects (44/52) had a hemostatic outcome of either “excellent” or “good”, the observation that the 8 subjects with a “poor” hemostatic outcome did not have different time course profiles of anti-fXa activity than the other subjects does not necessarily indicate no correlation between the effects of ANDEXXA on anti-fXa activity and hemostatic outcomes. To serve that purpose,

additional anti-fXa activity data from subjects that do not receive ANDEXXA should be provided for comparison.

8. INTEGRATED OVERVIEW OF SAFETY

Safety data from four studies with healthy volunteers (Studies 12-502, 14-503, 14-504 and 14-506) were pooled together, by dose and by ANDEXXA bolus only or ANDEXXA bolus plus infusion. Table 8 below summarizes treatment emergent adverse events (TEAEs) in the Safety Population. The incidence of related TEAEs appeared to be slightly higher in the ANDEXXA sets (21.6%-30.6%) compared to the pooled placebo set (18.1%). None of these TEAEs were severe or serious.

Table 8. Overview of Treatment-Emergent Adverse Events — Safety Population

Number (%) of Subjects with ≥ 1 TEAE	Andexanet Bolus Only			Andexanet Bolus Plus Infusion			Pooled Andexanet All Doses (N=223) ^a	Pooled Placebo (N=94)
	400-420 mg (N=62)	600-800 mg (N=51)	Combined Bolus Only (N=113)	400-420 mg plus Infusion (N=36)	720-800 mg plus Infusion (N=44)	Combined Bolus plus Infusion (N=80)		
Any TEAE	34 (54.8%)	27 (52.9%)	61 (54.0%)	17 (47.2%)	24 (54.5)	41 (51.3%)	120 (53.8%)	54 (57.4%)
Related to the Study Drug	16 (25.8%)	11 (21.6%)	27 (23.9%)	11 (30.6%)	10 (22.7%)	21 (26.3%)	58 (26.0%)	17 (18.1%)
TEAEs within the first hour of exposure to study drug	17 (27.4%)	10 (19.6%)	27 (23.9%)	6 (16.7%)	8 (18.2%)	14 (17.5%)	48 (21.5%)	17 (18.1%)
TEAEs of special interest	1 (1.6%)	1 (2.0%)	2 (1.8%)	0	0	0	3 (1.3%)	1 (1.1%)
TEAEs leading to premature discontinuation of drug	0	0	0	1 (2.8%)	0	1 (1.3%)	1 (0.4%)	0
Severe TEAEs	0	0	0	0	0	0	0	0
Serious TEAEs	0	0	0	0	0	0	0	0

Study 14-502 was a dose-ranging PK/PD study including all above dose regimens.

Subjects in Study 14-503 and Study 14-506 received 400mg or 400mg plus infusion.

Subjects in Study 14-504 received 800mg or 800mg plus infusion.

Source: Original BLA 125586/0; Summary of Clinical Safety, Table 2.7.4-11, p.48

There were no deaths and SAEs in any of the studies. One subject (Study 14-503 Part 2) in the ANDEXXA bolus plus infusion analysis set prematurely discontinued study drug after developing mild hives.

Because Study 14-505 enrolled diseased subjects while the above four studies enrolled healthy volunteers, this study was not included in above integrated overview. Table 9 below summarizes the TEAEs reported in this study, categorized by fXa inhibitor, in the safety population of 57 subjects. A total of 30 subjects experienced a total of 72 TEAEs. One subject (apixaban) with a non-serious TEAE of headache was considered as possibly related and another subject (rivaroxaban) with an SAE of ischemic stroke was assessed as probably related to ANDEXXA. There were eight deaths.

Table 9. Study 14-505 Overview of TEAE— Safety Population

Number (%) of Subjects	fXa Inhibitor			Andexanet Total N=57 (n%)
	Rivaroxaban n=24 (n%)	Apixaban n=27 (n%)	Enoxaparin n=6 (n%)	
Any TEAE	13 (54.1)	16 (59.3)	1 (16.7)	30 (52.6)
Related to the Study Drug	1 (4.2)	1 (3.7)	0 (0)	2 (3.5)
TEAEs of Special Interest	3 (12.5)	4 (14.8)	1 (16.7)	8 (14.0)
TEAEs Leading to Premature Discontinuation of Drug	0 (0)	0 (0)	0 (0)	0 (0)
Severe non serious TEAEs	0 (0)	2 (7.4)	0 (0)	2 (3.5)
Serious TEAEs	7 (29.2)	10 (37.0)	1 (16.7)	18 (31.6)
Fatal TEAEs ^a	3 (12.5)	4 (14.8)	0 (0.0)	7 (12.3)
Deaths	3 (12.5)	5 (18.5)	0 (0.0)	8 (14.0)

Source: Original BLA 125586/0/38; Clinical Overview, Table 2.5-9, p.71

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study results for two Phase 3 studies on healthy subjects (Studies 14-503 and 14-504) and one ongoing Phase 3b/4 study on the diseased population (Study 14-505) are summarized below, as well as integrated safety results on healthy volunteer subjects and safety results from Study 14-505.

- Study 14-503
 1. A total of 68 unique subjects received apixaban (34 in Part 1 and 34 in Part 2). Of these, 66 subjects were randomized (34 subjects in Part 1 [25 ANDEXXA, 9 placebo] and 32 in Part 2 [24 ANDEXXA, 8 placebo]).
 2. Significant difference of anti-fXa activity reduction (primary efficacy endpoint) was observed between subjects in the ANDEXXA and placebo groups. In Part 1, 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 Part 2, the mean percent change was -92.34% (2.81%) for the ANDEXXA group and -32.70% (5.58%) for the placebo group (p<0.0001). However, the duration

of reduction was around 2 and 4 hours after the bolus, for Part 1 and Part 2, respectively.

3. Statistical significance between groups was also achieved for all secondary efficacy endpoints, such as free apixaban concentration, and restoration of thrombin generation.
- Study 14-504
 4. A total of 80 unique subjects received rivaroxaban (41 in Part 1 and 39 in Part 2). All were randomized (Part 1 [27 ANDEXXA, 14 placebo] and Part 2 [26 ANDEXXA, 13 placebo]).
 5. In Part 1, the mean percent change of anti-fXa activity from baseline to the nadir was -92.22% (10.70%) for the ANDEXXA group and -17.08% (14.92%) for the placebo group ($p < 0.0001$). In Part 2, the mean percent change was -96.72% (1.84%) for the ANDEXXA group and -44.75% (11.75%) for the placebo group ($p < 0.0001$). Similar to Study 14-503, the duration of reduction was around 2 and 4 hours after the bolus, for Part 1 and Part 2, respectively.
 6. Statistical significance between groups was also achieved for all secondary efficacy endpoints, such as free rivaroxaban concentration, and restoration of thrombin generation.
 - Study 14-505
 7. As of June 9, 2016, 110 subjects have been enrolled and treated in this ongoing trial. Data from 52 subjects were evaluable for hemostatic efficacy. Among them, 44(84.6%) hemostatic outcomes were either “excellent” (37) or “good” (7). Only eight subjects had “poor” outcomes. Because all the subjects showed significant and similar reduction on the anti-fXa activity (See Appendix A), data of subjects who had small or no reduction in anti-fXa activity is lacking. Therefore, the available data from this study is not sufficient to conclude or rule out correlation between the effects of ANDEXXA on anti-fXa activity and hemostatic outcomes.
 - Safety
 8. In the pooled safety data from four studies (Studies 12-502, 14-503, 14-504 and 14-506), the incidence of related TEAEs appeared to be slightly higher in the ANDEXXA sets (21.6%-30.6%) compared to the pooled placebo set (18.1%). None of these TEAEs were severe or serious. There were no deaths and SAEs in any of the studies.
 9. In the safety population of 57 subjects in Study 14-505, there was one subject (apixaban) with a non-serious TEAE of headache considered

possibly related and one subject (rivaroxaban) with an SAE of ischemic stroke assessed as probably related to ANDEXXA. There were eight deaths.

- Comment to be included in the CR letter:

In your response dated July 5, 2016 (125586/0/52, response to statistics IR), for question 1c, you confirmed that the mITT set for the placebo group, part 1, included 14 subjects for Study 14-504. However, in response to question 1d, you acknowledged that only 13 subjects from the placebo group were included in the primary analysis based on mITT set. Please update this analysis (Study Report 14-504 [Part 1] Table 11) by including all 14 subjects, using the pre-specified missing data imputation method.

10.2 Conclusions and Recommendations

The results of the three reviewed studies were verified.

The following conclusions apply to Studies 14-503 and 14-504 (healthy volunteers):

- 1) These two studies won all the primary and secondary efficacy endpoints: significant difference of anti-fXa activity reduction was observed between subjects in the ANDEXXA and placebo groups, similarly for the free apixaban/rivaroxaban concentration, and restoration of thrombin generation.
- 2) In both studies, there was an apparent rebound of the anti-fXa activity in the ANDEXXA group. This short duration (2-4 hours) of reversal could be concerning.

The following finding applies to Study 14-505 (diseased population):

- 3) The available data from this study is not sufficient to conclude or rule out a correlation between the effects of ANDEXXA on anti-fXa activity and hemostatic efficacy

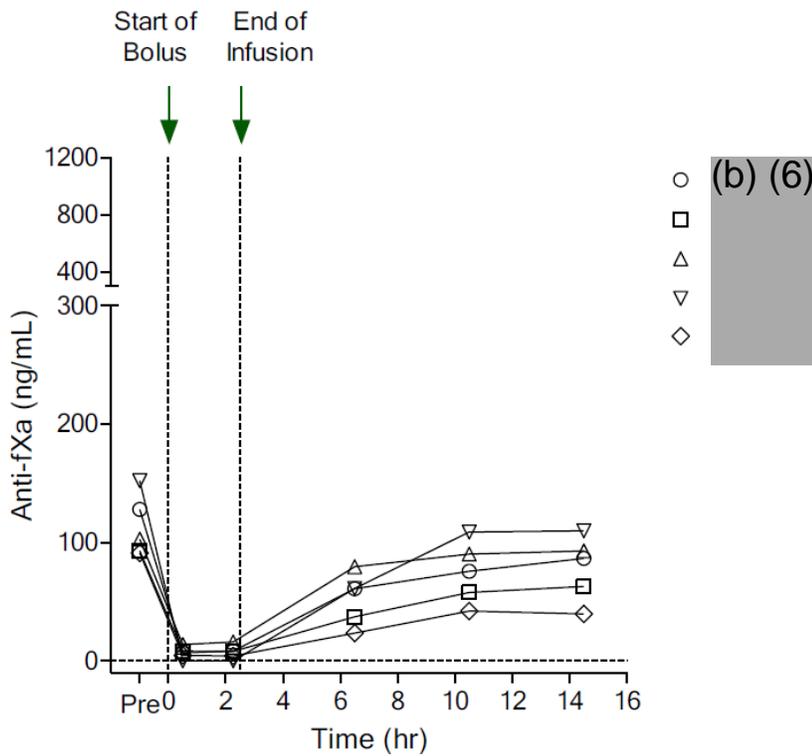
Most of the items included in the IR letter regarding some minor data inconsistencies were addressed by the applicant satisfactorily. One statistical comment will be included in the CR letter.

APPENDIX A: Time course profiles of anti-fXa activity in Study 14-505

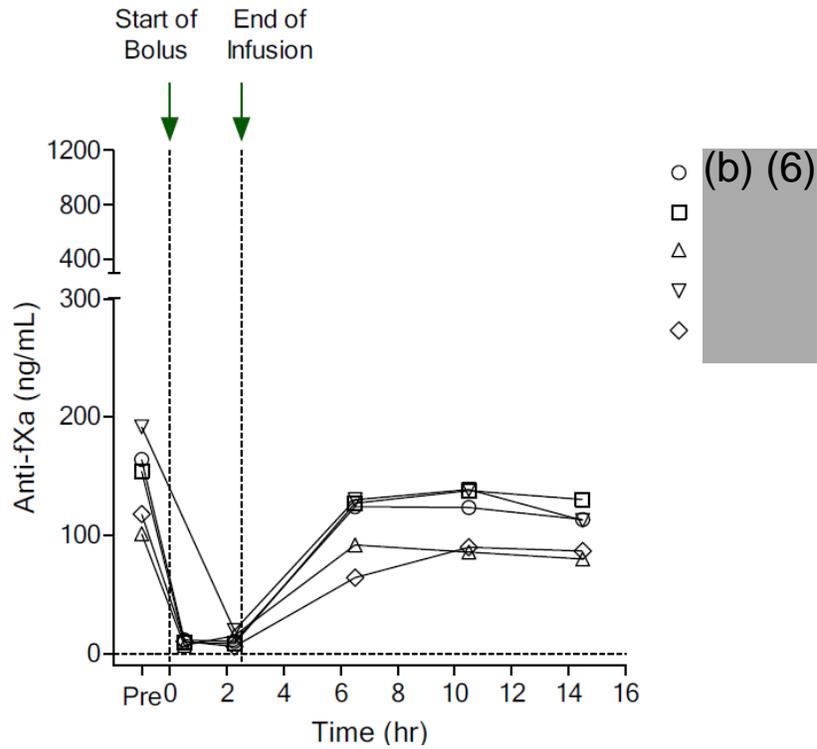
For clarity of data no more than five subjects are presented per figure. The source of these figures is Module 2.7.3 Summary of Clinical Efficacy from the Day 180 update, Amendment 38. The eight subjects with a “poor” adjudicated hemostatic outcome were highlighted in the figures. They didn’t show a different time course profile from those of subjects with an “excellent” or “good” outcome.

A. Subjects with Apixaban (total N=27)

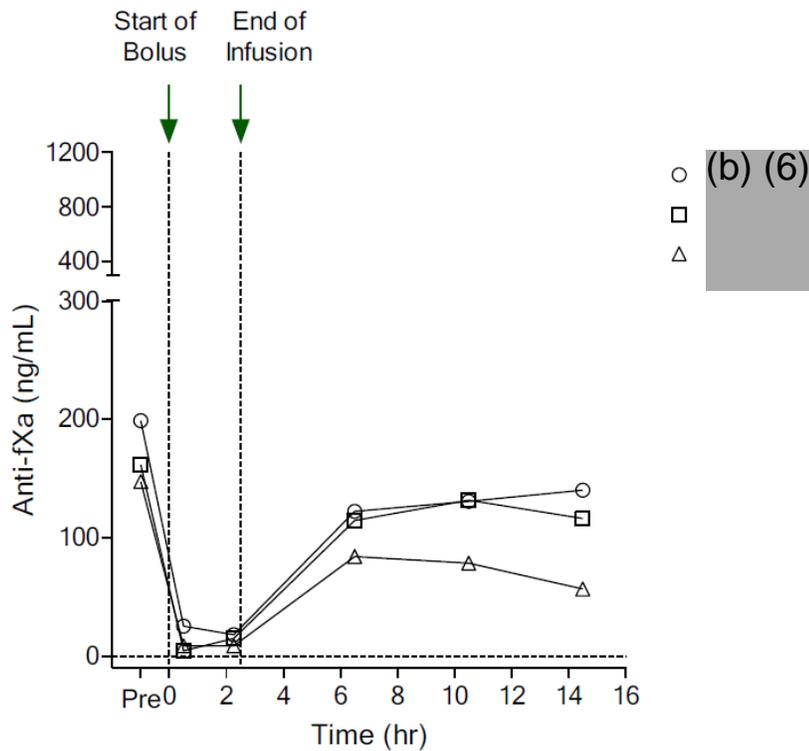
(a) Apixaban (Patients with baseline anti-fXa ≥ 75 ng/mL)



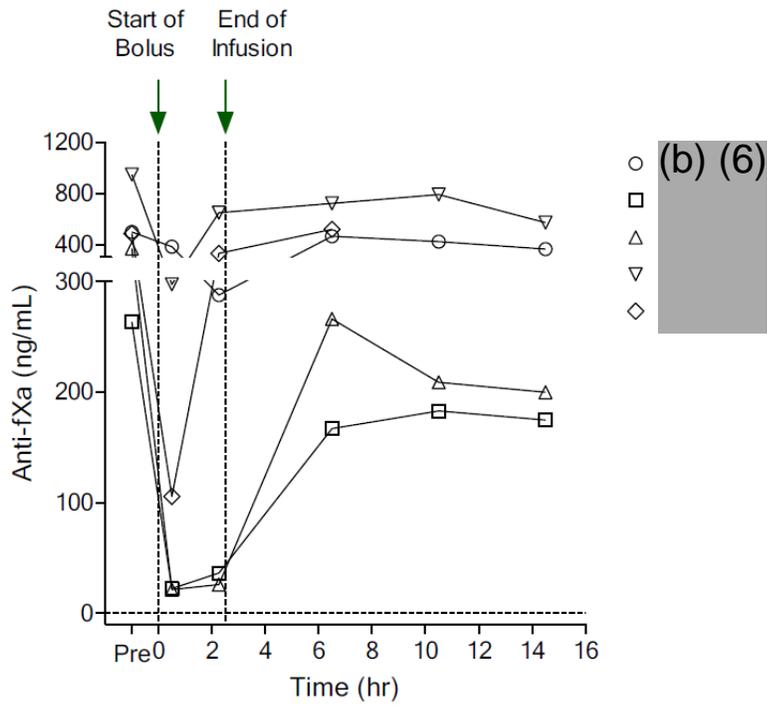
(b) Apixaban (Patients with baseline anti-fXa \geq 75 ng/mL)



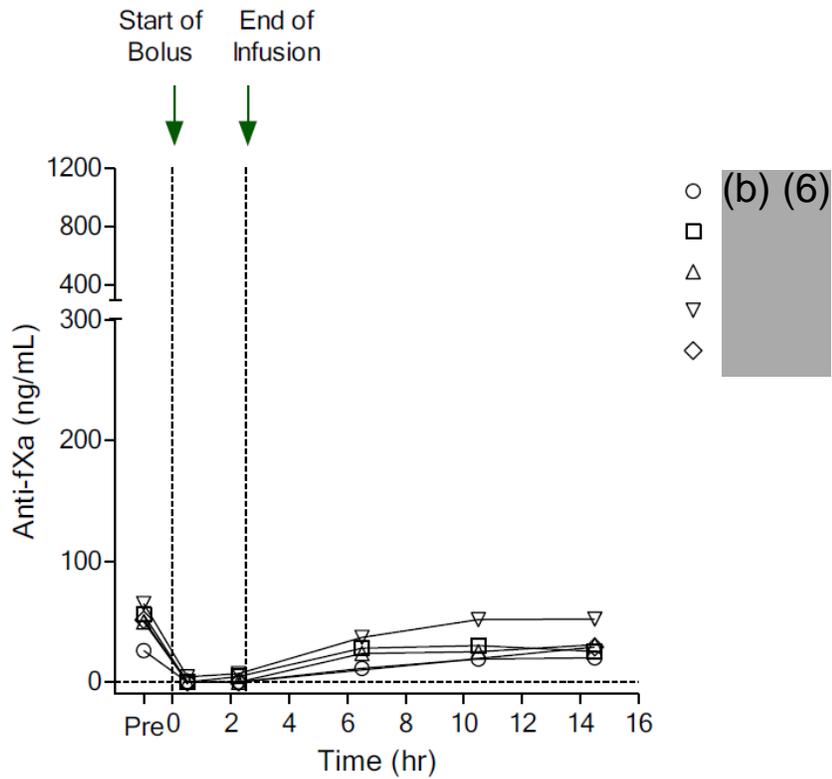
(c) Apixaban (Patients with baseline anti-fXa \geq 75 ng/mL)



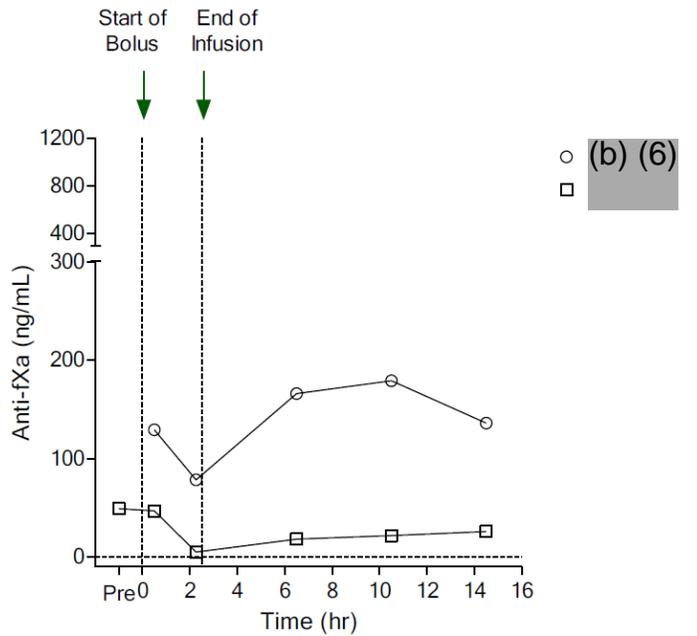
(d) Apixaban (Patients with the highest baseline anti-fXa levels)



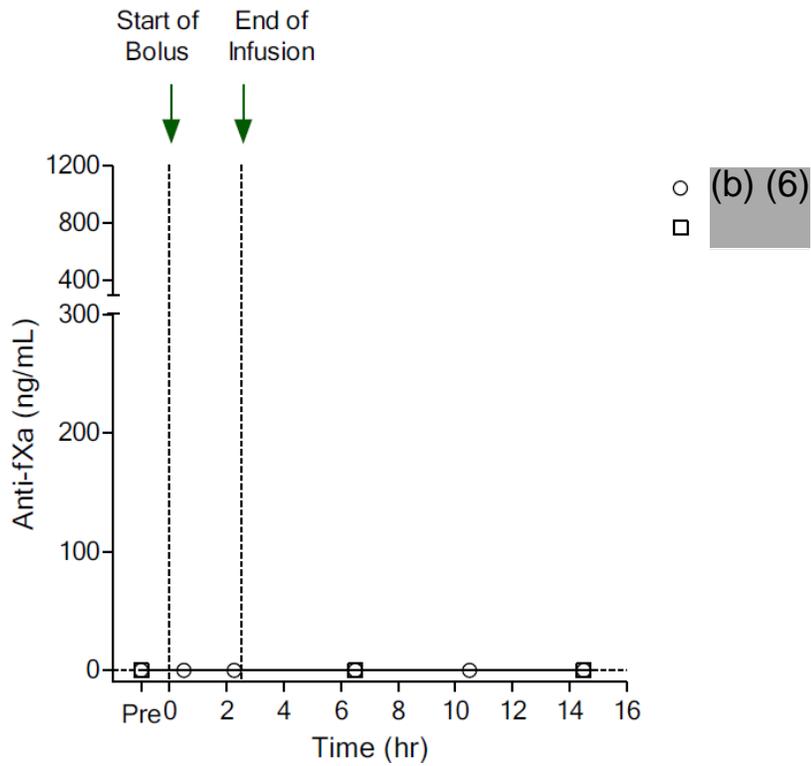
(e) Apixaban (Patients with baseline anti-fXa < 75 ng/mL)



(f) Apixaban (Patients with baseline anti-fXa < 75 ng/mL or data unavailable)

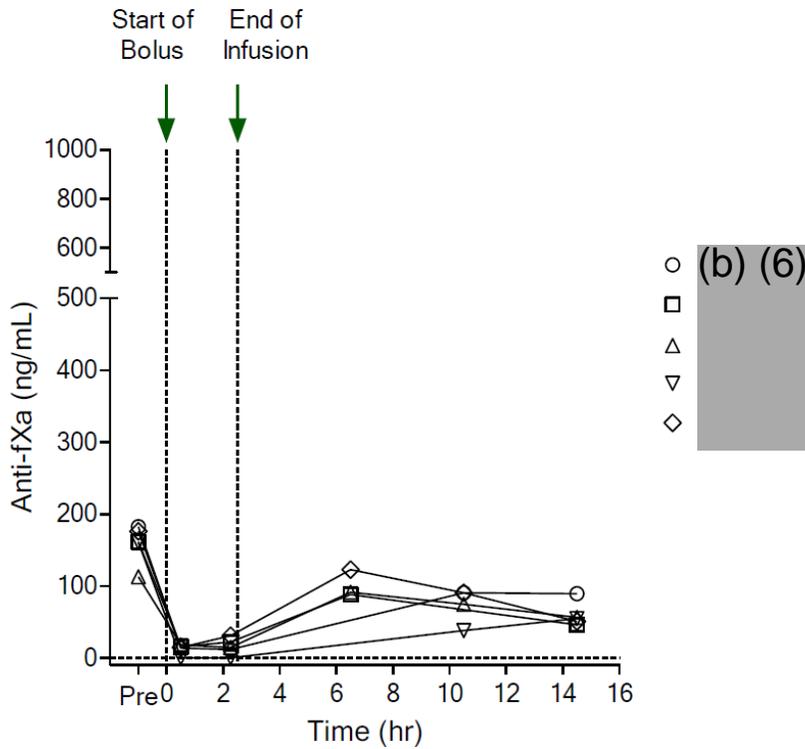


(g) Apixaban (Patients with baseline anti-fXa < 4.0 ng/mL)

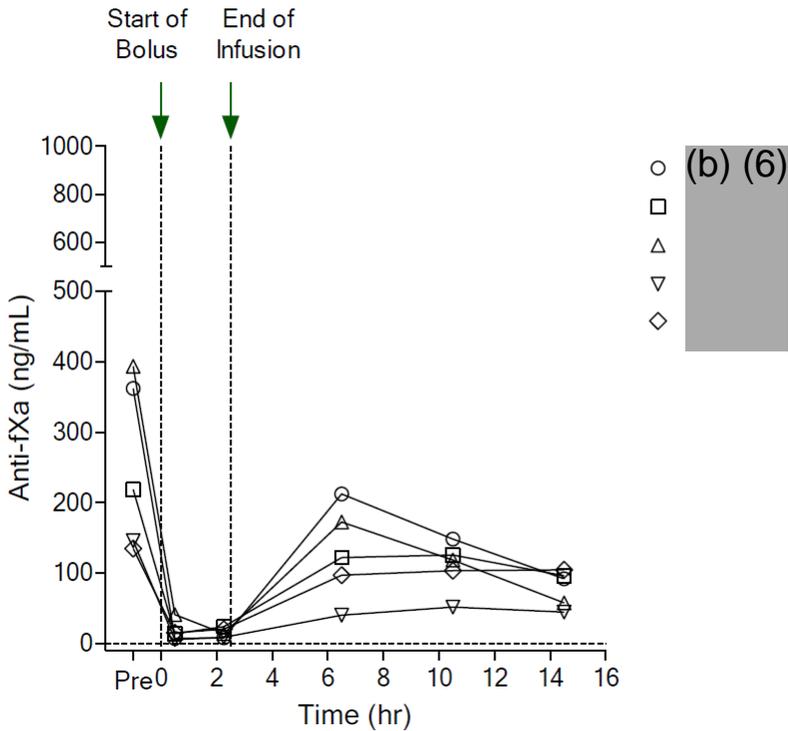


B. Subjects with Rivoroxaban (total N=24)

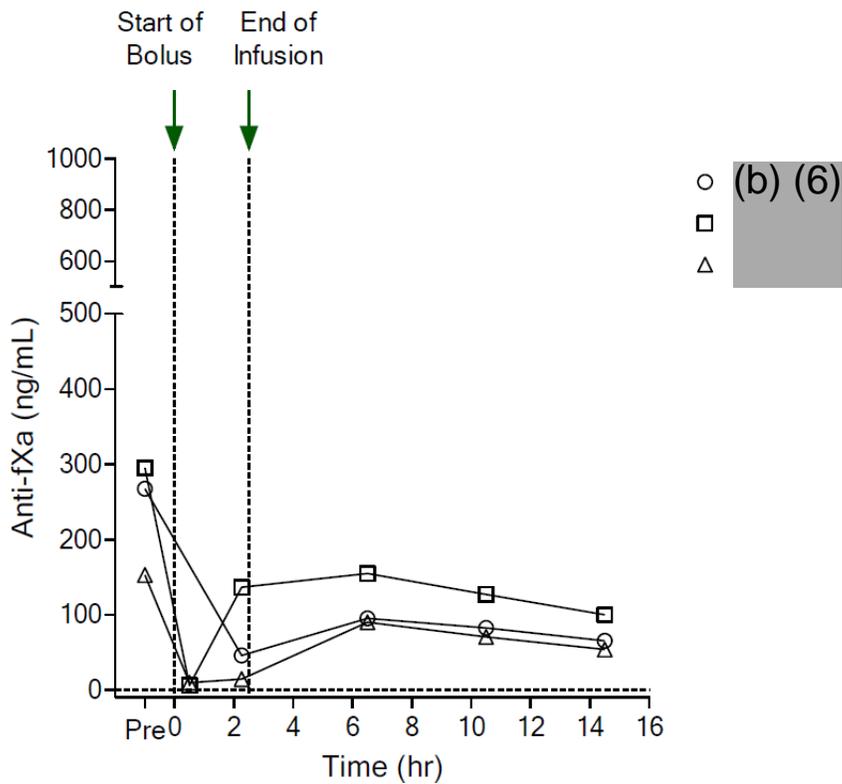
(a) Rivaroxaban (Patients with baseline anti-fXa ≥ 75 ng/mL)



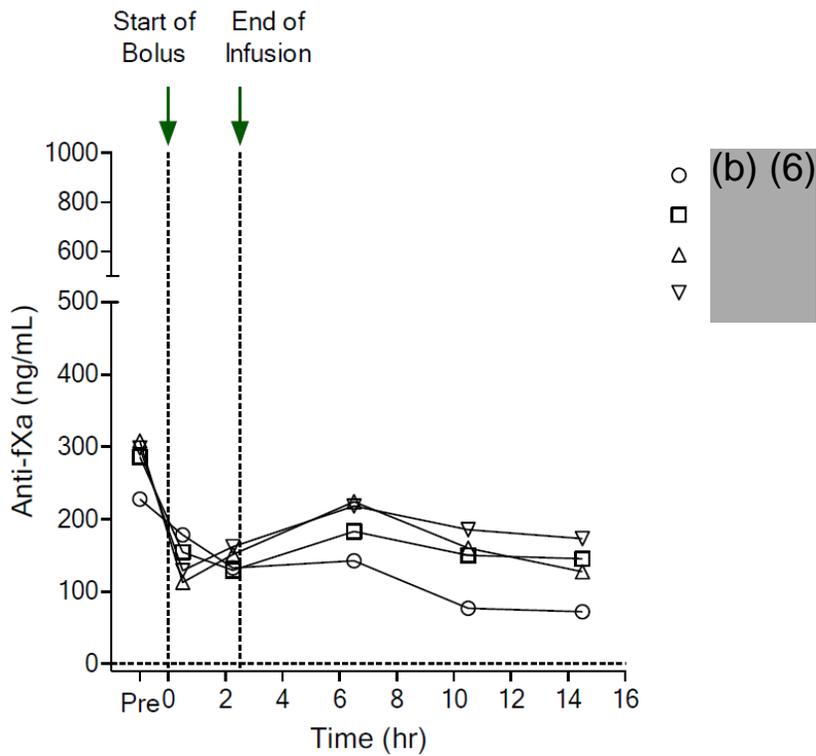
(b) Rivaroxaban (Patients with baseline anti-fXa ≥ 75 ng/mL)



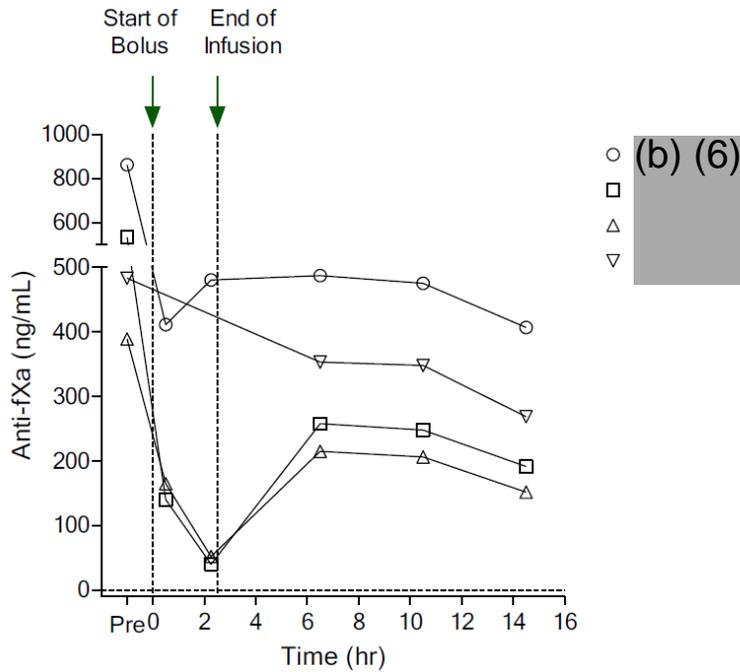
(c) Rivaroxaban (Patients with baseline anti-fXa ≥ 75 ng/mL)



(d) Rivaroxaban (Patients with baseline anti-fXa ≥ 75 ng/mL)

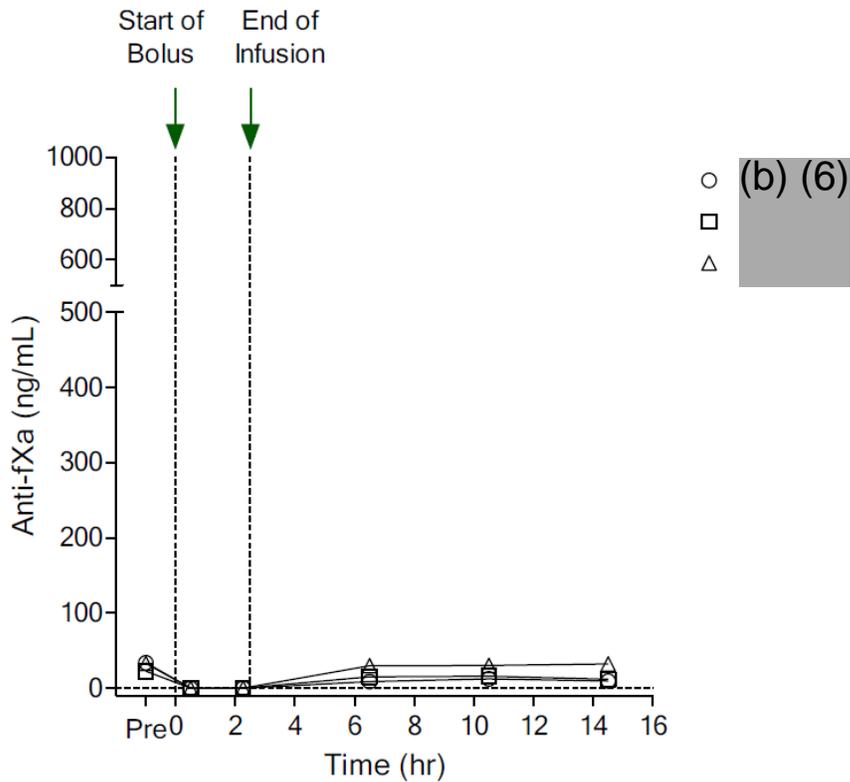


(e) Rivaroxaban (Patients with the highest baseline anti-fXa levels)



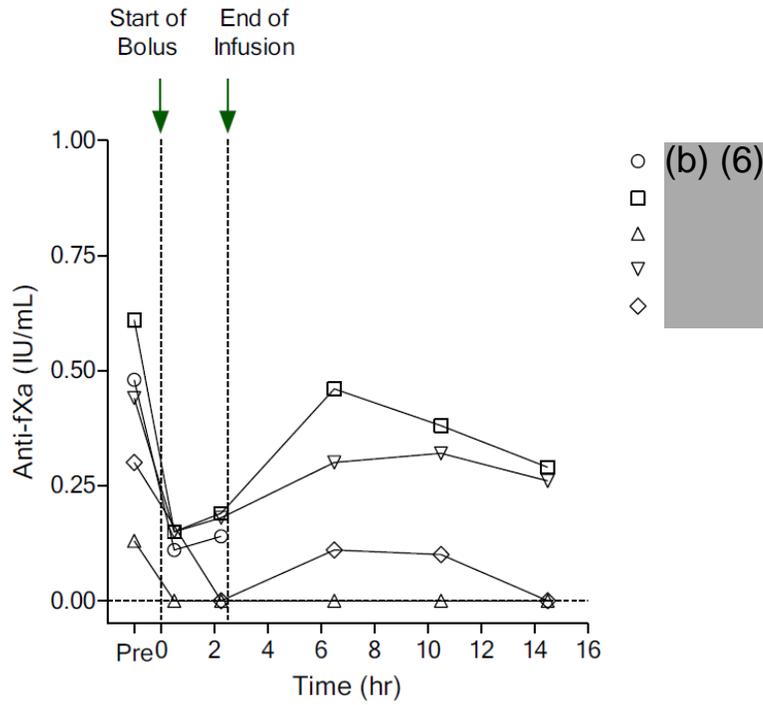
Note: subject “(b) (6)” had a missing outcome at 2 hours.

(f) Rivaroxaban (Patients with baseline anti-fXa < 4.0 ng/mL)



C. Subjects with Enoxaparin (total N=6)

(a) Enoxaparin (Patients with baseline detectable anti-fXa levels)



(b) Enoxaparin (Patient with baseline anti-fXa < 0.10 IU/mL)

