10/18/2024

FDA Briefing Document

sBLA# 125586/546

Drug name: Andexxa (coagulation factor Xa (recombinant), inactivated-zhzo)

Applicant: Astra Zeneca

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

November 21, 2024

DCEH/OCE/OTP

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Glossary

AA	accelerated approval
AC	Advisory Committee
Anti-FXa	anti-activated Factor Xa
BLA	Biologics Licensing Application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CT	computed tomography
DOAC	directly acting oral anticoagulant
EAC	endpoint adjudication committee
EQ-5D	EuroQoL-Group 5 Dimension
FDA	Food and Drug Administration
FXa	Factor X (ten), activated
GCS	Glasgow Coma Scale
IA	interim analysis
ICH	intracranial hemorrhage
ISTH	International Society on Thrombosis and Haemostasis
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NHLBI	National Heart, Lung, and Blood Institute
NIHSS	National Institute of Health Stroke Scale
PCC	prothrombin complex concentrate
PEP	primary efficacy population
PMR	postmarketing requirement
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental Biologics Licensing Application
TE	thrombotic event
TEAE	treatment-emergent adverse event
TFPI	tissue factor pathway inhibitor

UC	usual care
uw-mRS	utility-weighted modified Rankin Scale

1. Executive Summary

FDA initially granted accelerated approval (AA) of ANDEXXA, a recombinant modified human factor Xa (FXa) protein, in 2018, indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. AA was granted based on the change from baseline in anti-activated FXa (anti-FXa) activity, as a surrogate endpoint reasonably likely to predict clinical benefit as provided for in 21 CFR 601.41. As a condition of AA, AstraZeneca Inc. (Applicant) was required to conduct a randomized controlled trial to verify and describe the clinical benefit of ANDEXXA, due to uncertainty as to the relation of the surrogate endpoint to clinical benefit and of the observed clinical benefit to ultimate outcomes in the indicated population. On January 31, 2024, the Applicant submitted a supplemental Biologics Licensing Application (sBLA) for ANDEXXA with the results of the ANNEXA-I trial to fulfill this requirement.

FDA is convening this meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (AC) to discuss the results of the ANNEXA-I trial. FDA seeks the Committee's discussion of the benefits and risks of treatment with ANDEXXA, hereafter referred to as andexanet, in the indicated population. In particular, FDA is interested in the Committee's opinion regarding the increased risk of thrombosis relative to the benefits of treatment with andexanet.

In ANNEXA-I, patients who were receiving apixaban or rivaroxaban and who had severe intracranial bleeding, were randomized (1:1) to receive andexanet or usual care (UC) to achieve hemostasis. UC consisted of a prothrombin complex concentrate (PCC) in most patients in the UC arm, with 11% receiving no treatment as UC. Patients randomized to the andexanet arm received either a low dose or a high dose regimen, based on the timing and dosage of their last dose of rivaroxaban or apixaban, as per current approved dosage for andexanet.

The primary efficacy outcome measure in ANNEXA-I is a composite that consists of hematoma volume based on imaging, the NIH Stroke Scale (NIHSS) score, and use of rescue therapies, as assessed at 12 hours post-randomization. Patients were considered to have had successful hemostasis outcome if they had:

- ≤35% increase from baseline in hematoma volume;
- NIHSS score of less than + 7 change from the baseline score;
- No rescue therapy received between 3 and 12 hours post-randomization.

Non-evaluable patients were counted as having a non-effective (poor/none) outcome.

At the time of the interim analysis (IA) of ANNEXA-I (including patients randomized up to January 4, 2023 [inclusive]), the efficacy population consisted of 404 patients (andexanet arm, n=204; UC arm, n=200).

Treatment with andexanet demonstrated a statistically significant improvement in hemostasis compared to UC (andexanet: 65.7% versus UC: 53%; p-value of 0.011). The observed treatment difference between arms appears to be primarily driven by hematoma volume, with more patients in the andexanet arm compared to UC arm experiencing a ≤35% increase from baseline in hematoma volume at 12 hours (74% versus 60%). For the other components of the composite endpoint, outcomes were as follows: NIHSS change of less than + 7 from baseline at 12 hours was 88% versus 84%, and not having a need for rescue therapy was 98% versus 94% in the andexanet arm compared with the UC arm, respectively.

The major safety findings included a doubling of the rate of thromboses and thrombosis-related deaths at Day 30 in the andexanet arm compared with UC.

The major topics for discussion:

- Increased risk of thrombosis: ANNEXA-I demonstrated an increased incidence of thrombosis (14.6% versus 6.9%) and thrombosis-related deaths at Day 30 (2.5% versus 0.9%) in the andexanet arm compared with the UC arm, respectively. These findings raise concerns regarding whether the serious risks of treatment with andexanet are acceptable in the indicated population.
- Clinical meaningfulness of the benefit: While the primary efficacy endpoint in ANNEXA-I was met, the treatment difference across arms appears to be primarily driven by one of three components of the composite endpoint, namely the volume of hematoma at 12 hours, while other clinically meaningful endpoints (i.e., neurologic status at 24 hours, modified Rankin Scale [mRS] at Day 30, and overall mortality) were not different between the two arms. These findings raise the question as to whether the benefit demonstrated in ANNEXA-I outweighs the serious risks.

2. Background

2.1. Anticoagulant Associated Bleeding

Directly acting oral anticoagulants (DOACs) have become the predominant class of anticoagulants used in the United States (Wheelock et al. 2021); their use may be complicated by major bleeding, the most serious adverse reaction occurring in 2% to 4% of patients per year (Cormier and Siegal 2024). Bleeding can be associated with high morbidity and mortality, especially with intracranial hemorrhage (ICH) (Providencia et al. 2014).

2.1.1. Treatment for Anticoagulant Associated Bleeding

Routinely available laboratory tests (e.g., PT/aPTT) cannot be used to measure the degree of anticoagulation following treatment with DOACs. Therapeutic options available to treat DOAC-associated bleeding are limited. Andexanet (Greenberg et al. 2022) was granted AA for the reversal of DOACs in patients with major bleeding.

Additionally, off-label use of PCCs is an option for some patients. Therefore, there remains an unmet medical need for safe and effective treatments for DOAC-related major bleeding.

2.2. Product Description

In normal hemostasis, coagulation FXa, generated by either the extrinsic or intrinsic coagulation cascade, along with FVa forms the prothrombinase complex (FXa-FVa) on the surface of activated platelets, resulting in the generation of thrombin and subsequent formation of a fibrin clot. Andexanet is a genetically modified variant of human FXa that lacks the proteolytic activity of native FXa needed to catalyze a coagulation reaction. Andexanet has two mechanisms by which it exerts its pro-coagulant effects:

1. Binds with high affinity to FXa inhibitors serving as a decoy to sequester the agents out of the plasma, thus lowering anti-FXa activity. The reduction of anti-FXa activity was dose-dependent within the dose range of 30 to 800 mg of andexanet. Following the recommended low and high doses of andexanet, the anti-FXa activity returned to placebo levels after approximately 2 hours after completion of a continuous infusion.
2. Binds and inactivates tissue factor pathway inhibitor (TFPI), the only known inhibitor of tissue factor (TF), a transmembrane glycoprotein responsible for the initiation of coagulation at the site of vascular injury. The anti-TFPI action requires 100 to 1000-fold lower drug concentrations of andexanet than the concentration required for lowering anti-FXa activity, so no dose-dependency was observed (neither the magnitude nor the duration) within the 30 to 800 mg dose range. TFPI activity in plasma returns to the pretreatment levels approximately 96 hours following andexanet administration.

While both mechanisms are expected to contribute to therapeutic (hemostasis) and pathologic (thrombosis) effects, the relative contribution of each in the mechanism of action of andexanet is unclear.

The following two dosing regimens of andexanet, depending on the timing and dosage of the last dose of rivaroxaban or apixaban, were approved under AA (Table 1 and Table 2).

Table 1. Dosing Regimens of Andexanet

Dose	Initial IV Bolus	Follow-on IV Infusion
Low	400 mg at a target rate of 30 mg/min for ~15 minutes	480 mg at a target rate of 4 mg/min for 120 minutes
High	800 mg at a target rate of 30 mg/min for up to ~30 minutes	960 mg at a target rate of 8 mg/min for 120 minutes

Source: The United States Prescribing Information (USPI) of ANDEXXA
Abbreviations: IV, intravenous

Table 2. Dose of Andexanet Based on Timing and Dosage of Last Dose of Rivaroxaban or Apixaban

FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

Source: The United States Prescribing Information (USPI) of ANDEXXA

At the time of AA, the dosing algorithm was determined to target an 80% to 90% reduction of anti-FXa activity at the end of a 2-hour infusion based on the model-based prediction. Of note, with these dosing regimens, the median of >90% reduction in anti-FXa activity was shown in ANNEXA-4 in patients with bleeding.

2.3. Regulatory History

The original BLA for andexanet was submitted in 2015. For brevity, selected milestones since approval in 2018 are included here.

- May 3, 2018: FDA granted AA to andexanet for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This approval was based on the surrogate endpoint of decrease in anti-FXa activity in two healthy volunteer studies and efficacy results from 35 of a planned 477 patients with bleeding (diverse bleeding sites) in the single-arm ANNEXA-4 study. A postmarketing requirement (PMR) randomized, controlled study, ANNEXA-I, was required.
- April16, 2020: Applicant submitted protocol Amendment 1 for the required PMR study, ANNEXA-I. FDA reviewed and provided feedback on October 5, 2020, questioning the appropriateness of the primary efficacy endpoint of hemostasis at 12 hours following treatment in this confirmatory study. FDA stated that the clinical outcome should be measured at a later timepoint, recommending mRS or Glasgow Outcome Score at 90 days as acceptable primary outcome measures. These were not implemented in the protocol.
- December 18, 2020: Applicant submitted sBLA 125586/207 based on data from ANNEXA-4 to expand the indication to patients treated with edoxaban and enoxaparin. Complete response letter issued due to lack of demonstration of effectiveness.
- January 28, 2021: Applicant submitted a protocol amendment for ANNEXA-I, proposing changes to the sample size from 440 to 900, based on newly

published data suggesting that the UC arm would have a 65% to 70% success rate of the primary endpoint of hemostasis at 12 hours, thus necessitating a larger study population to demonstrate superiority.

- January 31, 2024: Applicant submitted sBLA 25586/546 based on data from ANNEXA-I study to fulfill the PMR requirement.

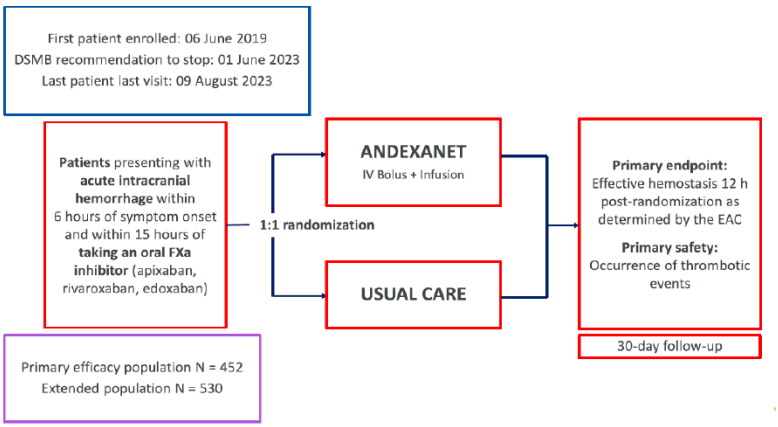
3. ANNEXA-I Trial

The primary evidence of safety and efficacy for this sBLA derives from the ANNEXA-I trial.

3.1. Study Design and Study Population

The key design features and procedures for the ANNEXA-I trial are shown below in Figure 1 and Figure 2.

Figure 1. ANNEXA-I Study Design Schema



Source: Applicant slide deck application orientation meeting March 7, 2024
Abbreviations: DSMB, Data and Safety Monitoring Board; EAC, endpoint adjudication committee

ANNEXA-I was conducted across 131 centers in 23 countries in Europe and North America. Patients were stratified at randomization by timing of baseline imaging (<180 minutes versus ≥180 minutes). Another stratification factor in the study was intended Usual care agent (PCC versus non-PCC), however the data was not collected for the first half of the study; thus, the protocol was amended to remove this stratification factor from the primary statistical analyses. Crossover in the was not permitted.

Patient randomization was to occur within 15 hours of last administered dose of the DOAC. However, if time from last DOAC was >15 hours or unknown but an anti-FXa level was measured within 2 hours prior to consent and the value was >100 ng/mL, patients were deemed eligible for the study.

The key study eligibility criteria for ANNEXA-I include the presence of the following:

- Acute intracerebral bleeding (non-tumor related) with estimated blood volume ≥ 0.5 mL and ≤ 60 mL;
- Head computed tomography (CT) or magnetic resonance imaging (MRI) scan demonstrating bleeding within 2 hours prior to randomization;
- Treatment with rivaroxaban or apixaban <15 hours prior to randomization; if local anti-FXa activity was >100 ng/mL, patients were eligible if last dose was >15 hours or unknown;
- Time from bleeding symptom onset <6 hours prior to baseline imaging;
- NIHSS ≤ 35 and Glasgow Coma Scale (GCS) ≥ 7;
- No thrombotic event (TE) within last 2 weeks.

The eligibility criteria were intended to enroll a study population at risk for hematoma expansion and for whom treatment would likely demonstrate a benefit.

While the study included edoxaban- and enoxaparin-treated patients, these patients were excluded from the FDA efficacy and safety analyses as the data were not relevant to the approved indication.

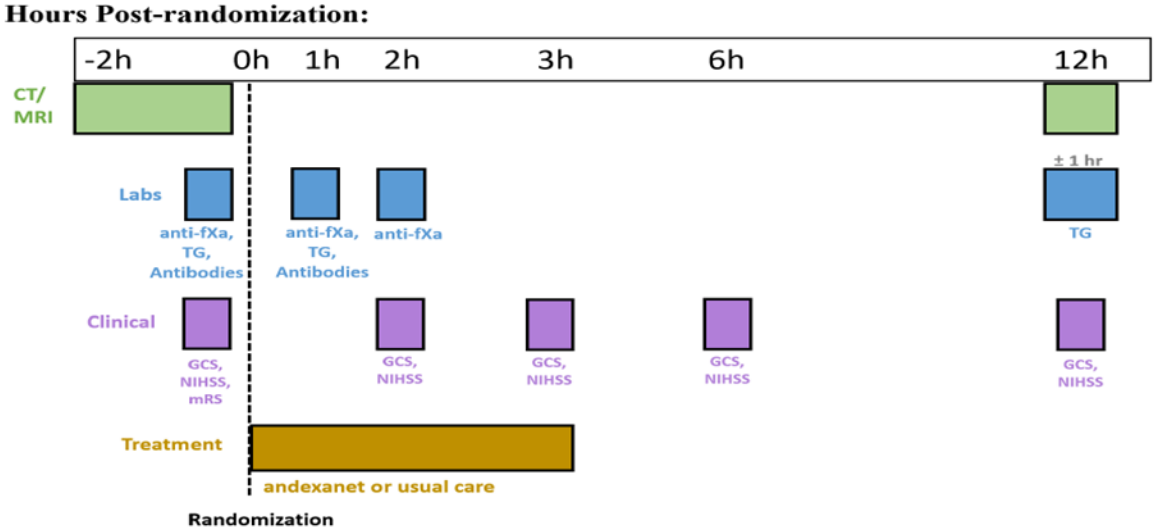
3.2. Study Treatment

Patients in the trial were randomized to receive treatment as follows:

- Andexanet arm: Andexanet dosing based on Table 1 and Table 2. Patients whose time from last DOAC was >15 hours or unknown received a high dose of andexanet. Andexanet was to be initiated no later than 30 minutes after randomization and ideally within 2 hours from baseline brain imaging. Patients could be treated with any rescue medications other than andexanet, as deemed clinically necessary by the investigator.
- Usual care (UC) arm: Any treatment other than andexanet, initiated within 3 hours post-randomization; this could include no treatment. It was at the investigator's discretion what type of usual care treatment, if any, was given.

Study procedures pre- and post-randomization are illustrated in Figure 2 below.

Figure 2. Events Through First 12 Hours After Enrollment



Source: ANNEXA-I Protocol 2 July 2018, page 30
Abbreviations: CT, computed tomography; GCS, Glasgow Coma Scale, MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale.

3.3. Study Objectives and Endpoints

Trial Objectives

Efficacy: The primary objective was to evaluate the effect of andexanet versus usual care on the rate of effective hemostasis.

The secondary efficacy objective was to evaluate the effect of andexanet versus usual care on anti-FXa activity.

Key additional efficacy objectives include:

- Evaluate the effect of andexanet versus usual care on neurologic function.
- Assess the relationship between anti-FXa activity and the achievement of hemostatic efficacy.
- Evaluate the effect of andexanet versus usual care on health-related quality of life.

Safety: The key safety objectives were to evaluate the occurrence of TEs at 30 days after randomization, and to evaluate in-hospital and 30-day mortality rate (all-cause, cardiovascular, and bleeding).

Primary Efficacy Endpoint

The primary efficacy endpoint was effective hemostasis 12 hours post-randomization, as determined by the blinded endpoint adjudication committee (EAC), based on 3 components:

- Brain imaging to assess hematoma expansion.

- NIHSS evaluation of acute clinical outcome.
- Need for rescue medication.

The determination that effective hemostasis (good/excellent; successful outcome) was achieved was based on the requirement that all of the following criteria were met:

a. No greater than 35% increase (for good 21% to ≤35% and for excellent ≤20%) from baseline in hematoma volume at 12 hours post-randomization.
b. NIHSS score of less than +7-point change from the baseline score at 12 hours post-randomization.
c. Have not received rescue therapy between 3- and 12-hours post-randomization.

The assessment of hematoma volume expansion was read by two independent readers. If the hemostatic efficacy category or primary bleed location differed between the two readers, then a third reader did an independent analysis. The final reading determination was based on alignment from two readers. If there was uncertainty with the validity of the scan measurements, the case was escalated to the adjudication committee.

To achieve “excellent” hemostasis categorized as excellent, patients were required to have a hematoma volume increase of ≤20 % and criteria b and c above. To achieve “good” hemostasis, patients were required to have a hematoma volume increase of 21% to ≤35% and criteria b and c above.

Secondary Efficacy Endpoint

Percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization.

The secondary efficacy endpoint was to be tested sequentially after a statistically significant effect was found for the primary efficacy endpoint. The alpha level was to be the same as that used for the primary efficacy endpoint.

Additional Select Efficacy Endpoints

Proportion of neurologic deterioration, as defined by an NIHSS score increase ≥4 or a GCS score decrease ≥2 at 24 hours post-randomization versus baseline.

Change from baseline in mRS score at 30 days post-randomization.

Select Safety Endpoints

ANNEXA-I safety endpoints included the following: TEs confirmed by adjudication through 30 days, and 30-day all-cause, cardiovascular, and bleeding mortality.

3.4. Study Analysis Plan

ANEXXA-1 was designed to test the statistical superiority of andexanet versus UC in achieving effective hemostasis. One IA was planned to evaluate the primary efficacy

after 50% of the patients had been adjudicated for hemostatic efficacy. The IA could lead to early stopping of the study due to efficacy or futility following pre-specified stopping rules. A sample size re-estimation was also planned using the promising zone approach. To control the overall Type I error rate at 5%, the study employed an alpha spending function by the Lan and DeMets method based on Pocock boundaries (DeMets and Lan 1994). Specifically, the alphas allocated to the interim and final analyses were to be 0.031 and 0.0277, respectively.

3.4.1. Efficacy Analysis

The primary efficacy analysis was performed in the primary efficacy population (PEP) analysis set, which included all participants randomized to andexanet. Efficacy was analyzed in keeping with the intent-to-treat principle. Participants who were randomized without signing the consent form throughout the study were not included in the PEP set. The PEP analysis set included 404 patients, with 204 in the andexanet arm and 200 in the UC arm.

The original protocol was dated July 2, 2018. There were 3 amendments following this date. Amendment 1 was dated April 15, 2020, with pertinent changes including:

1. Site of hematoma was limited to intracerebral. All intracranial bleeding was included prior to this date. The rationale for this change was to improve hematoma volume size estimation by imaging.
2. The time from bleeding symptom onset to baseline imaging was decreased from 12 to 6 hours so patients enrolled were at greatest risk of hematoma volume increase.
3. Tumor-related bleeding was excluded to decrease heterogenicity of mechanism of bleeding.
4. Exclusion criteria for patients with NIHSS score >35 was added to be able to assess clinical benefit.
5. Sample size was increased from 440 to 900 patients.

Amendment 2 was dated July 29, 2021, with pertinent changes including:

1. Exclusion criteria for patients with hematoma volume <0.5 mL added so patients enrolled had greatest risk of hematoma volume increase.
2. Pre-planned sample size re-estimation at IA was added to increase the statistical power.
3. Neurologic function efficacy endpoint was re-categorized from a secondary endpoint to an additional efficacy endpoint.

Amendment 3 was dated December 1, 2022, with pertinent changes including:

1. The stratification of intended usual care was removed from the SAP as it was not collected prior to Amendment 1.

3.5. Study Results

ANNEXA-I met its efficacy endpoint success criterion at the time of pre-planned IA with 50% (~450 of 900) of the planned patients, leading to stopping of the study. At the time of the IA, a total of 404 patients had been randomized who had received apixaban and rivaroxaban (andexanet arm, n=204; UC arm, n=200). The extended population consisted of 474 patients, with 241 in the andexanet arm and 233 in the UC arm.

Analyses of ANNEXA-I were performed on two different populations: a PEP which included patients randomized by the time of the IA, and the extended population which included all patients randomized until end of study. The efficacy analysis for ANNEXA-I is based on the PEP. The extended population was used for safety analyses and for sensitivity analyses for efficacy.

3.5.1. Efficacy Results

Patient baseline demographics on ANNEXA-I are shown below in Table 3.

Table 3. Baseline Demographic in the Primary Efficacy Population

Demographic Characteristic	Andexanet (N=204)	Usual Care (N=200)	Total (N=404)
Age (years)	-	-	-
Mean (SD)	78.8 (8.48)	78.8 (8.63)	78.8 (8.54)
Median (IQR)	80.0 (11.0)	80.0 (11.0)	80.0 (11.0)
Min, Max	48, 96	42, 96	42, 96
Age group (years), n (%)	-	-	-
<65	12 (5.9)	13 (6.5)	25 (6.2)
65-74	41 (20.1)	42 (21.0)	83 (20.5)
≥75	151 (74.0)	145 (72.5)	296 (73.3)
Sex, n (%)	-	-	-
Male	114 (55.9)	98 (49.0)	212 (52.5)
Race, n (%)	-	-	-
Asian	3 (1.5)	3 (1.5)	6 (1.5)
Black or African American	5 (2.5)	3 (1.5)	8 (2.0)
White	182 (92.4)	185 (93.0)	367 (92.7)
Other	7 (3.6)	8 (4.0)	15 (3.8)
Missing	7	1	8
Ethnicity, n (%)	-	-	-
Hispanic or Latino	10 (4.9)	10 (5.0)	20 (5.0)
Not Hispanic or Latino	175 (85.8)	178 (89.0)	353 (87.4)
Not Reported	14 (6.9)	11(5.5)	25 (6.2)
Unknown	5 (2.5)	1 (0.5)	6 (1.5)
Region, n (%)	-	-	-
Europe	178(87.3)	175 (87.5)	353 (87.4)
North America	26 (12.7)	25 (12.5)	51 (12.6)

Source: Adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Table 14.1.2.1a
Abbreviations: IQR, interquartile range; PEP, primary efficacy population; SD, standard deviation

Patient baseline characteristics on ANNEXA-I are shown below in Table 4.

Table 4. Baseline Characteristics in the Primary Efficacy Population

Characteristic	Andexanet (N=204)	Usual Care (N=200)	Total (N=404)
Patients receiving apixaban	140/204 (68.6%)	135/200 (67.5%)	275/404 (68.1%)
Patients receiving rivaroxaban	64/204 (31.4%)	65/200 (32.5%)	129/404 (31.9%)
Intracerebral bleeding	179/203 (88.2%)	186/199 (93.5%)	365/402 (90.8%)
Spontaneous bleeding	178/204 (87.3%)	170/200 (85%)	(348/404) (86.1%)
Traumatic bleeding	26/204 (12.7%)	30/200 (15%)	56/404 (13.9%)
Average hematoma volume	-	-	-
Mean (SD)	18.08 (20.85) mL	16.81 (21.85) mL	17.45 (21.33) mL
Median	11.10 mL	8.59 mL	9.72 mL
Indication for treatment: atrial fibrillation	174/204 (85.3%)	165/200 (82.5%)	339/404 (83.9%)
Baseline imaging <180 minutes	118/204 (57.8%)	121/200 (60.5%)	239/404 (59.2%)
Baseline imaging ≥180 minutes	86/204 (42.2%)	79//200 (39.5%)	165/404 (40.8)

Source: Adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Tables 14.1.1.2a, 14.1.3.1a, 14.1.3.2a

Table 5 shows the treatment received per population, with the majority of patients in the andexanet group receiving a low dose.

Table 5. Treatment Received Within the Primary Efficacy Population

Treatment	Andexanet (N=204) n/N (%)	Usual Care (N=200) n/N (%)
High dose	38/204 (19%)	NA
Low dose	162/204 (79%)	2/200 (1%)
PCC	1/204 (0.5%)	174/200 (87%)
Other	NA	2/200 (1%)
No treatment	3/204 (1.5%)	22/200 (11%)

Source: FDA reviewer calculations from ADSL dataset
Abbreviations: PCC, prothrombin complex concentrate; PEP, primary efficacy population.

Primary Efficacy Endpoint

Andexanet showed a statistically significant advantage on the primary efficacy endpoint of hemostatic efficacy at 12 hours, as shown in Table 6 below.

Table 6. Primary Efficacy Endpoint Outcomes and Each Component by Treatment Group in the Primary Efficacy Population

Component	Andexanet	Usual Care	Difference	p-value
Effective hemostasis	134/204 (66%)	106/200 (53%)	12%	0.011
Hematoma volume ≤35% increase*	150/204 (74%)	119/200 (60%)	13%	-
NIHSS change less than + 7 from baseline	170/194 (88%)	159/190 (84%)	4%	-
No rescue therapy	199/204 (98%)	187/200 (94%)	4%	-

Source: FDA reviewer calculations from ADEFF, ADSL, ADRS datasets, and adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Tables 14.2.1.1a, 14.2.3.6a, 14.2.3.7.2a
* excellent = ≤20% and good = 21 to ≤35%. Andexanet had 123/204 (60.3%) excellent and 11/204 (5.4%) good. UC had 93/200 (46.5%) excellent and 13/200 (6.5%) good
Abbreviations: NIHSS, National Institute of Health Stroke Scale; PEP, primary efficacy population

Secondary Efficacy Endpoint

The percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization was > 90%. This was observed among patients anticoagulated with both apixaban and rivaroxaban regardless of hemostatic efficacy as shown in Table 7.

Table 7. Percent Change From Baseline to Nadir in Anti-FXa Activity by Treatment, Hemostatic Efficacy, and Prior FXa Inhibitor in the Primary Efficacy Population

Hemostatic Efficacy	Andexanet N=179 Excellent/ Good	Andexanet N=179 Poor/ None	Usual Care N=171 Excellent/ Good	Usual Care N=171 Poor/ None
Apixaban	-	-	-	-
n	90	37	64	53
Median (Range)	-94.5 (-99.1, 672)	-93.8 (-98.0, 1805)	-20.0 (-97.9, 416)	-20.8 (-94.4, 128)
Rivaroxaban	-	-	-	-
n	32	20	24	30
Median (Range)	-95.6 (-99.1, -3.2)	-97.3 (-98.8, -52.8)	-44.5 (-95.9, 298)	-47.8 (-93.8, 26.1)

Source: FDA reviewer calculations from ADLB and ADEFF datasets

Additional Select Efficacy Endpoints

Proportion of Neurologic Deterioration, as defined by an NIHSS score increase ≥4 or a GCS score decrease ≥2 at 24 hours post-randomization versus baseline

Exploratory analyses of neurologic deterioration at 24 hours in the responders for both arms are shown in Table 8.

Table 8. Neurologic Deterioration at 12 and 24 Hours in the Primary Efficacy Population

Timepoint	Andexanet	Usual Care	Andexanet Responders	Usual Care Responders
12 hours	24/194 (12%)	31/190 (16%)	N/A	N/A
24 hours	39/124 (31%)	35/121 (29%)	12/77 (16%)	3/60 (5%)

Source: FDA reviewer calculations from ADEFF, ADSL and ADRS datasets
*Neurologic deterioration at 12 hours is defined as an increase of ≥ 7 point from baseline to 12 hours in NIHSS.
*Neurologic deterioration at 24 hours is defined as NIHSS increase ≥ 4 at 24 hours compared to baseline, or GCS score decrease ≥ 2 at 24 hours compared to baseline.
*Responders are patients with excellent or good outcome; non-responders are patients with poor/none outcome
Abbreviations: PEP, primary efficacy population

Change From Baseline in mRS Score at 30 Days Post-Randomization

A mRS score of 0 to 3 was evaluated because this is defined as functionally independent; scores of 4 to 6 reflect functional dependence.

Table 9. Modified Rankin Scale in Primary Efficacy Population

Parameter	Andexanet	Usual Care
mRS 0-3 (baseline)	161/198 (81%)	156/194 (80%)
mRS 0-3 (Day 30)	54/189 (29%)	64/192 (33%)
Patients with baseline mRS 0-3	-	-
mRS remained 0-3 at Day 30	48/151 (32%)	59/151 (39%)
mRS changed to 4-6 at Day 30	103/151 (68%)	92/151 (61%)
Patients with baseline mRS 4-6	-	-
mRS remained 4-6 at Day 30	29/33 (88%)	33/36 (92%)
mRS changed to 0-3 at Day 30	4/33 (12%)	3/36 (8%)

Source: FDA reviewer calculations from ADSL, ADQS datasets, and adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Tables 14.2.3.3.1a.
Abbreviations: mRS, modified Rankin Scale; PEP, primary efficacy population.

A logistic regression of Day 30 independence status resulted in an odds ratio (95% CI) of 1.30 (0.81, 2.09), comparing the andexanet arm with the UC arm. In addition, a subgroup analysis based on change in functional status from baseline to 30 days was also performed. Among patients with baseline mRS scores of 0 to 3 (functionally independent), 68% (103/151) of patients changed to a score of 4 to 6 (functionally dependent) at 30 days in the andexanet arm, versus 61% (92/151) of patients in the UC arm. The sample size in the subgroup of patients with baseline mRS score of 4 to 6 was too small to provide interpretable information.

We also evaluated change in mRS indicative of change in functional status from baseline to 30 days in both responders and non-responders.

Table 10. Change in Modified Rankin Scale in Responders Between Treatment Groups in the Primary Efficacy Population

Parameter	Andexanet Responders	Usual Care Responders
Patients with baseline mRS 0-3	-	-
mRS remained 0-3 at Day 30	41/100 (41%)	45/76 (59%)
mRS changed to 4-6 at Day 30	59/100 (59%)	31/76 (41%)
Patients with baseline mRS 4-6	-	-
mRS remained 4-6 at Day 30	19/23 (83%)	20/23 (87%)
mRS changed to 0-3 at Day 30	4/23 (17%)	3/23 (13%)

Source: FDA reviewer calculations from ADSL, ADQS datasets
Abbreviations: mRS, modified Rankin Scale; PEP, primary efficacy population.

Protocol Deviations/Missing Data

Protocol deviations and missing data in ANNEXA-I are shown in Table 11.

Table 11. Summary of Protocol Deviations or Missing Data*

Reason	Andexanet N=204	UC N=200	Total N=404
>6 to 12 hours (depending on protocol version) between stroke symptoms and baseline imaging	4 (2%)	2 (1%)	6 (1%)
Baseline hematoma volume missing or outside eligible hematoma volume range	14 (7%)	11 (6%)	25 (6%)
Anti-FXa activity levels missing or <100 ng/mL in patients whose last dose of apixaban or rivaroxaban was >15 hours or unknown	10 (5%)	10 (5%)	20 (5%)
Imaging and NIHSS at baseline or at 12-hours >1 hour out of window, not done, or time unknown	23 (11%)	33 (17%)	56 (14%)
Baseline or 12-hour NIHSS unblinded or read by untrained reader	8 (4%)	6 (3%)	14 (3%)
Incorrect treatment administered	2 (1%)	2 (1%)	4 (1%)
Patient randomized in error	3 (1%)	0	3 (1%)

*Of note, there are 15 (3%) additional subjects with discrepancies amongst 3 readers of hematoma volume expansion; 5 (2%) in andexanet arm and 8 (4%) in UC arm
Source: FDA reviewer analysis based on ADSL, ADAE, ADDV, ADEFF, ADEX, ADPR, ADRS and ADLB datasets
Abbreviations: NIHSS, National Institute of Health Stroke Scale; UC, usual care

Table 12 shows response rate (per treatment received) for both dose groups compared to all UC.

Table 12. Patients Receiving High Dose vs. Low Dose Compared to Usual Care in the Primary Efficacy Population

Dose	Responders n/N (%)	Non-Responders n/N (%)
High dose	19/38 (50%)	19/38 (50%)
Low dose	115/162 (71%)	47/162 (29%)
Usual care	106/200 (53%)	94/200 (47%)

Source: FDA reviewer calculations from ADEFF dataset
Abbreviations: PEP, primary efficacy population.

3.5.2. Safety Results

Analyses of safety focused on assessment of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), mortality, hospitalization data, clinical laboratory parameters, and vital signs. Safety data was analyzed descriptively. Thrombotic events and deaths were reported for adjudication by an EAC blinded to treatment. Patients were analyzed for safety based on actual treatment received.

The safety analysis population consists of all patients enrolled in ANNEXA-I with follow-up to the end of the study. This included a total of 471 patients (andexanet, n=239; UC, n=232). Demographics of the safety population are shown in Table 13.

Table 13. Demographics by Treatment Group (Safety Population)

Parameter	Andexanet Arm N=239	Usual Care Arm N=232
Median age (Range) years	81 (48-96)	80 (42-96)
Male sex, (%)	(53.6)	(51%)
Race/ethnicity, (%)	-	-
White	(93.9)	(93)
Black/African American	(1.7)	(1.8)
Asian	(1.3)	(1.8)
Other	(3)	(3.5)

Source: FDA reviewer calculations from ADSL dataset

Most Common Adverse Events

The most common (≥5%) adverse events are shown in Table 14. TEAEs were reported at comparable rates in the two arms: 85.8% of patients in the andexanet arm versus 81.9% in the usual care arm.

Table 14. Treatment-Emergent Adverse Events With Incidence Rate ≥ 5% (Safety Population)

Preferred Term/Group Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Any TEAE	205 (85.8)	190 (81.9)
Urinary tract infection	48 (20.1)	40 (17.2)
Hypokalemia	38 (15.9)	23 (9.9)
Constipation	37 (15.5)	23 (9.9)
Pneumonia	37 (15.5)	32 (13.8)
Pneumonia aspiration	29 (12.1)	21 (9.1)
Delirium	20 (8.4)	27 (11.6)
Headache	22 (9.2)	18 (7.8)
Nausea	22 (9.2)	16 (6.9)
Pyrexia	21 (8.8)	19 (8.2)
Intracranial hemorrhage*	21 (8.8)	30 (12.9)
Vomiting	9 (3.8)	14 (6)
Hypertension	18 (7.5)	12 (5.2)
Insomnia	14 (5.9)	7 (3)
Ischemic stroke**	21 (8.8)	3 (1.3)

Source: Reviewer calculations, ADAE dataset. In summarizing n (%), if a patient had multiple events for a particular PT, he/she is counted only once for that PT.
PTs are coded using MedDRA version 25.1.
Intracranial hemorrhage* Group Term includes: Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke, Intracranial haematoma , Intraventricular haemorrhage, Subarachnoid haemorrhage, Subdural haematoma
Ischemic stroke** Group Term includes: Cerebellar stroke, Cerebral infarction, Cerebral ischaemia, Cerebrovascular accident, Ischaemic stroke
For patients who were randomized to usual care arm and received no treatment, adverse events that occurred after randomization were considered as TEAEs.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; PT, preferred term; TEAE, treatment-emergent adverse event.

Serious Adverse Events (SAEs)

Table 15. Treatment-Emergent Serious Adverse Events, Frequency >1% of Patients (Safety Population)

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Cardiac disorders	-	-
Cardiac failure	3 (1.3)	0
Myocardial infarction*	11 (4.6)	2 (0.9)
Infections and infestations	-	-
Pneumonia	11 (4.6)	15 (6.5)
Pneumonia aspiration	11 (4.6)	7 (3)
Sepsis	6 (2.5)	2 (0.9)
Urinary tract infection	3 (1.3)	1 (0.4)
Nervous system disorders	-	-
Neurologic decompensation	2 (0.8)	7 (3)
Cerebral hematoma	3 (1.3)	2 (0.9)
Cerebral hemorrhage	7 (2.9)	11 (4.7)
Hemorrhage intracranial	6 (2.5)	9 (3.9)
Hydrocephalus	7 (2.9)	4 (1.7)
Ischemic stroke	12 (5)	1 (0.4)
Renal and urinary disorders	-	-
Acute kidney injury	3 (1.3)	0
Psychiatric disorders	-	-
Delirium	2 (0.8)	3 (1.3)
Respiratory, thoracic, and mediastinal disorders	-	-
Acute respiratory failure	3 (1.3)	1 (0.4)
Pulmonary embolism	4 (1.7)	7 (3)
Respiratory failure	3 (1.3)	4 (1.7)

Source: reviewer calculations from ADAE dataset. In summarizing n (%), if a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs and PTs are coded using MedDRA version 25.1.
For patients who are randomized to usual care group and receive no treatment, adverse events that occur after randomization are considered as TEAEs.
Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; PT, preferred term; SOC, system organ class; TESAE, treatment-emergent serious adverse event. *includes Myocardial infarction and Acute myocardial infarction

Deaths

Data on deaths were collected through Day 30. Per protocol, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurred within 12 hours post randomization was not to be regarded as an AE or SAE, except where there was evidence to suggest a causal relationship with study drug. In such patients, the cause of death was not reported as a TEAE, thus, the overall number of deaths in the study is greater than the number of patients who had TEAEs leading to death. A total of 67 (28%) patients in the andexanet group died, of whom 59 were reported as having a TEAE leading to death, and 61 (26.3%) patients in the usual care group died, of which 49 were reported as having a TEAE leading to death. Table 16 shows deaths by cause among the 59 patients in the andexanet arm reported as having a TEAE leading to death, and 50 patients in the usual care arm reported as having a TEAE leading to death. Death related to thrombotic events through 30 days post-randomization occurred

in 6 patients (2.5%) in the andexanet arm compared with 2 patients (0.9%) in the UC arm.

Table 16. Treatment-Emergent Adverse Events Leading to Death, Frequency ≥ 0.8% of Patients (Safety Population)

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Cardiac disorders	-	-
Cardiac failure	3 (1.3)	0
Infections and infestations	-	-
Pneumonia	5 (2.1)	6 (2.6)
Pneumonia aspiration	6 (2.5)	5 (2.2)
Sepsis	3 (1.3)	1 (0.4)
Injury, poisoning and procedural complications	-	-
Brain Herniation	0	2 (0.9)
Nervous system disorders	-	-
Intracranial hemorrhage*	12 (5)	18 (7.8)
Hydrocephalus	2 0.8)	1 (.0.4)
Ischemic stroke**	4 (1.7)	2 (0.9)
Neurological decompensation	1 (0.4)	2 (0.9)
Respiratory, thoracic, and mediastinal disorders	-	-
Pulmonary embolism	3 (1.3)	1 (0.4)
Respiratory failure	3 (1.3)	4 (1.7)

Source: Reviewer calculations, ADAE dataset
In summarizing n (%), if a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs and PTs are coded using MedDRA version 25.1. For patients who are randomized to usual care group and receive no treatment, adverse events that occur after randomization are considered as TEAEs.
Abbreviations: CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment group; n, number of patients included in analysis; PT, preferred term; SOC, system organ class; TEAE, Treatment-Emergent Adverse Event. Intracranial hemorrhage* Group Term includes: Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, Haemorrhagic stroke, Intracranial haematoma, Intracranial hemorrhage, Intraventricular haemorrhage,Subarachnoid haemorrhage, Subdural haematoma. Ischemic stroke** Group Term includes: Cerebellar stroke, Cerebral infarction, Cerebral ischaemia, Cerebrovascular accident, Ischaemic stroke

Hospitalization Rates

Table 17 shows hospitalization outcomes for the two treatment arms.

Table 17. Treatment Arm vs. Hospitalization Outcomes (Safety Population)

Parameter	Andexanet Patients	Usual Care Patients
Median days hospitalized, n (range)	12 (1-50)	11 (1-45)
Patients readmitted, n	6	5
Days in intensive care unit, n (range)	7 (1-30)	5 (1-40)

Source: Reviewer calculated from ADHO dataset.

Adverse Events of special Interest (AESI)

The AESI for ANNEXA-I were TEs. TEs are discussed in detail in the next section 3.5.3.

3.5.3. Incidence of Thrombotic Events

The rate of TEs among patients treated with andexanet is double the rate of those who were treated with UC. This difference is statistically significant and clinically relevant; of 239 patients treated with andexanet, 35 (14.6%) suffered TEs versus 16 (6.9%) of the

232 patients in the UC arm, (p-value = 0.0048). Table 18 lists TEs summarized by system organ class and preferred term.

Table 18. Thrombotic Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Any thrombotic event	35 (14.6)	16 (6.9)
Cardiac disorders	12 (5)	2 (0.9)
Atrial thrombosis	1 (0.4)	0
Myocardial infarction*	11 (4.6)	2 (0.9)
General disorders	0	1 (0.4)
Sudden cardiac death	0	1 (0.4)
Investigations	0	1 (0.4)
Troponin increased	0	1 (0.4)
Nervous system disorders	21 (8.8)	4 (1.7)
Cerebellar stroke	1 (0.4)	0
Cerebral ischemia	1 (0.4)	0
Cerebral infarction	1 (0.4)	2 (0.9)
Cerebral venous thrombosis	0	1 (0.4)
Cerebrovascular accident	4 (1.7)	0
Ischemic stroke***	14 5.9)	1 (0.4)
Renal and urinary disorders	1 (0.4)	0
Renal infarct	1 (0.4)	0
Respiratory, thoracic, and mediastinal disorders	4 (1.7)	7 (3)
Pulmonary embolism	4* (1.7)	7 (3)
Vascular disorders	4 (1.7)	3 (1.3)
Arterial occlusive disease	0	1 (0.4)
Deep vein thrombosis	1 (0.4)	2 (0.9)
Embolism arterial	1** (0.4)	0
Femoral artery embolism	1 (0.4)	0
Peripheral ischemia	1 (0.4)	0

Source: FDA reviewer calculations from ADAE dataset
In summarizing n (%), if a patient had multiple events for a particular SOC or PT, he/she is counted only once for that SOC or PT. SOCs and PTs are coded using MedDRA version 25.1.
For patients who are randomized to UC group and receive no treatment, adverse events that occur after randomization are considered as TEAEs. N, number of patients in treatment group;
*Group Term: Includes one patient with Respiratory distress and one patient with Respiratory failure which were adjudicated as Pulmonary embolism, as well as two patients with PT of Pulmonary embolism. **Reported case of arterial thrombosis adjudicated as TE, patient (b) (6) .*** Includes strokes by imaging only. * includes Myocardial infarction, Acute myocardial infarction
Abbreviations: PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Timing of Thrombotic Events in ANNEXA-I

Thrombotic events occurred earlier in the andexanet arm compared to the UC arm: median of 3.5 days from randomization (range 1 to 24) in the andexanet arm, compared with median of 16 days from randomization (range 2 to 25) in the UC arm. Of the 35 andexanet-treated patients who experienced a thrombotic event, 18 (53%) had the TE during the first 3 days, compared with 1 of 16 patients (6.3%) in the UC group. Early onset of TEs may preclude attempts at prophylactic anticoagulant resumption due to the risk of bleeding.

Incidence of Thrombotic Events Following Re-initiation of Anticoagulation

After hemostasis has been achieved in a patient who is bleeding, safe resumption of anticoagulation is a treatment goal to prevent thromboses. A total of 165 patients (69%) in the andexanet arm and 163 patients (70.3%) in the UC arm received at least one dose of anticoagulation as a prophylactic measure, following study treatment. The median time to resumption of anticoagulation in ANNEXA-I was 5 days following study treatment. Overall, 9.6% (16 of 165) of patients in the andexanet arm and 5.5% (9 of 163) of patients in the UC arm who received at least one dose of anticoagulation following study treatment, subsequently developed TEs. These 16 patients comprised 45.7% of all patients to develop a TE in the andexanet arm (N=35; see Table 18) which may suggest limited effectiveness of prophylactic anticoagulation.

For the patients who did not receive any anticoagulant as a prophylactic measure following study treatment, andexanet treatment was associated with 2.5 times the rate of TEs compared with UC. A total of 19 of the 74 patients (26.4%) in the andexanet arm experienced a TE, compared to 7 of the 69 patients (10.1%) in the UC arm. Please see Table 19.

Table 19. Thrombotic Events in Patients With or Without Re-Anticoagulation (Safety Population)

Parameter	Andexanet (N=239)	Usual Care (N=232)
Patients who received at least one dose of any anticoagulant as a prophylactic measure, n	165	163
Patients with thrombotic events, n (%)	16 of 165 (9.6)	9 of 163 (5.5)
Patients who did not receive any anticoagulation as a prophylactic measure, n	74	69
Patients with thrombotic events, n (%)	19 of 74 (26.4)	7 of 69 (10.1)

Source: FDA reviewer calculations from ADAE dataset

4. Topics for Discussion

4.1. Increased Risk of Thrombosis of Treatment with Andexanet

The rate of thrombotic events among patients treated with andexanet is double the rate of those who were treated with UC. Of patients treated with andexanet, 14.6% suffered TEs versus 6.9% in the UC arm.

Thrombotic events in the andexanet arm tended to occur earlier at median day 3.5, compared with median day 16 in the UC arm. Such early TE onset may preclude attempts at prophylactic anticoagulant resumption.

Of those patients who resumed prophylactic anticoagulation, 9.6% in the andexanet arm and 5.5% in the UC arm developed TEs. More than half of the 35 patients experiencing a TE after andexanet treatment had their first TE within 3 days of randomization, a period when anticoagulation is generally not feasible due to bleeding concerns, and therefore did not receive prophylactic anticoagulation. Furthermore, the effectiveness of prophylaxis may be limited, as nearly half of the 35 andexanet arm patients (Table 18)

who developed a TE had already restarted prophylactic anticoagulation prior to developing the TE. Overall, given the early onset of TEs in the andexanet arm (>50% within 72 hours after treatment), and the limited effectiveness of prophylactic anticoagulation, thrombotic risk appears challenging to mitigate.

Death rates were comparable between the treatment arms with 28.0% in the andexanet group and 26.3% in the UC arm, however, deaths attributable to TEs were more twice as high in the andexanet arm than in the UC arm.

4.2. Clinical Benefit of Treatment with Andexanet

ANNEXA-I demonstrated that treatment with andexanet has a statistically significant advantage on the primary efficacy endpoint of hemostatic efficacy at 12 hours at an observed rate of 66% versus a rate 53% observed for UC. A difference in the primary efficacy endpoint in favor of andexanet was statistically significant (12.2% difference with a p-value of 0.011). Success of the primary endpoint was largely driven by one component: volume of hematoma at 12 hours. The other two components were similar in both arms.

The percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization, was > 90%. This reduction was observed among patients anticoagulated with both apixaban and rivaroxaban, and regardless of outcome.

Although andexanet showed superiority of the primary efficacy endpoint over UC within the PEP population, the superior efficacy at 12 hours did not predict longer-term benefit. The primary efficacy endpoint was intended to capture hematoma expansion but does so only at an earlier timepoint than is recommended in National Heart, Lung, and Blood Institute (NHLBI) guidelines and thus may fail to capture delayed hematoma expansion. Additionally, hematoma expansion was characterized as a dichotomized response, which may be an inadequate approach to fully capturing the potential treatment effect on hematoma volume. There was also a lack of imaging data beyond 12 hours in the sBLA submission, precluding the assessment of bleeding and/or thrombotic events beyond 12 hours.

Determination of whether subsequent intercurrent events, like bleeding progression or ischemic strokes, were the cause of the deterioration was not possible in the absence of this data beyond 12 hours.

The neurologic outcomes that are evaluated in the endpoints are also optimally evaluated at later timepoints as recommended by the ISTH. Clinical guidelines emphasize the importance of clinical outcomes measured 30 to 180 days after ICH, thus, the clinical meaningfulness of the statistically significant improvement on the primary efficacy endpoint is difficult to assess in absence of the benefits at later timepoints. The clinical review team considers GCS or mRS at 90 days to be more informative of clinical benefit and was relayed to the Applicant during protocol review. In absence of assessment of these measures at 90 days, the review team regards

neurologic deterioration at 24 hours and disability measured by mRS at 30 days to be more relevant measures of longer-term clinical benefit. This is based on NHLBI guidelines of recommendations for primary outcomes for clinical trials evaluating hemostatic agents in patients with ICH. A greater number of patients in the andexanet arm had worse outcomes in these endpoints compared to the UC arm.

5. Draft Discussion Questions

1. While the primary efficacy endpoint in ANNEXA-I was met, the treatment difference across arms appears to be primarily driven by one of three components of the composite endpoint. Discuss whether the treatment effect on the study's primary efficacy endpoint constitutes clinical benefit.
2. ANNEXA-I demonstrated an increased incidence of thrombosis (15.1% versus 6.9%) and thrombosis-related deaths at Day 30 (2.5% versus 0.9%) in the andexanet arm compared to the UC. Are the serious risks of andexanet acceptable in the indicated population and in the context of the benefit demonstrated in ANNEXA-I?

6. References

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7. Appendix

ANNEXA-I Inclusion Criteria:

1. Written informed consent.
2. Age ≥18 years old at the time of consent.
3. An acute intracerebral bleeding episode, defined as an estimated blood volume of ≥0.5 mL to ≤60 mL acutely observed radiographically within the cerebrum. Patients may have extracerebral (e.g., subdural, subarachnoid, epidural) or extracranial (e.g., gastrointestinal, intraspinal) bleeding additionally, but the intracerebral hemorrhage must be considered the most clinically significant bleed at the time of enrollment.
4. Performance of a head CT or MRI scan demonstrating the intracerebral bleeding within 2 hours prior to randomization (the baseline scan may be repeated only once to meet this criterion).
5. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], or edoxaban [last dose 30 mg or greater]:
   - ≤15 hours prior to randomization.
   - >15 hours prior to randomization or unknown time of last dose, only if 1) the local anti-FXa activity >100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban or edoxaban), and 2) the local anti-FXa activity level is obtained within 2 hours prior to consent, performed as per standard of care. Note: Patients enrolled in this manner should receive a high andexanet dosing regimen.
6. Time from bleeding symptom onset <6 hours prior to the baseline imaging scan.
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy for 30 days after the last dose of study drug.
8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
9. NIHSS score ≤35 at the time of consent.

ANNEXA-I Exclusion Criteria:

1. Planned surgery, including Burr holes for hematoma drainage, within 12 hours after randomization. Minimally invasive surgery/procedures not directly related to the treatment of intracranial bleeding and that are not expected to significantly affect hematoma volume are allowed (e.g., Burr holes for intracranial pressure monitoring, endoscopy, bronchoscopy, central lines—Section 7.2, Section 7.3, and Appendix G).
2. Glasgow Coma Scale (GCS) score <7 at the time of consent. If a patient is intubated and/or sedated at the time of consent, they may be enrolled if it can be documented that they were intubated/sedated for non-neurologic reasons within 2 hours prior to consent.

3. Anticipation that the baseline and follow up brain scans will not be able to use the same imaging modalities (i.e., patients with a baseline CT scan should have a CT scan in follow up; similarly, for MRI).
4. Expected survival of less than 1 month (not related to the intracranial bleed).
5. Recent history (within 2 weeks) of a diagnosed TE or clinically relevant symptoms of the following:
    - Venous Thromboembolism (VTE: e.g., deep venous thrombosis, pulmonary embolism [PE], cerebral venous thrombosis), myocardial infarction (MI), Disseminated Intravascular Coagulation (DIC), cerebral vascular accident, transient ischemic attack (TIA), acute coronary syndrome, or arterial systemic embolism (see Appendix H for DIC scoring algorithm).
6. Acute decompensated heart failure or cardiogenic shock at the time of randomization (see Appendix I for cardiogenic shock definition).
7. Severe sepsis or septic shock at the time of randomization (see Appendix I for sepsis definition).
8. The patient is a pregnant or lactating female.
9. Receipt of any of the following drugs or blood products within 7 days prior to consent:
    - Vitamin K Antagonist (VKA) (e.g., warfarin).
    - Dabigatran.
    - PCC products (e.g., KCentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®), or anti-inhibitor coagulant complex (e.g., FEIBA®), FFP, and whole blood.
10. Past use of andexanet (or planned use of commercial andexanet).
11. Treatment with an investigational drug < 30 days prior to consent.
12. Any tumor-related bleeding.
13. Known hypersensitivity to any component of andexanet.

NIHSS definition: The NIHSS is a widely used standardized stroke scoring system to determine stroke severity. It is used both clinically and within clinical trials. It measures neurologic function using a 15-item scale and evaluates performance in 11 categories with scores ranging from 0 to 42. The categories include level of consciousness, gaze, visual fields, facial palsy, limb mobility and ataxia, sensory, language, dysarthria, extinction, and inattention. Within the ANNEXA-I study, individuals were trained to perform NIHSS and blinded to patient's treatment allocation.

mRS definition: mRS is a commonly used outcome measure in stroke treatment trials. It measures functional independence on a seven-grade scale seen below in Table 20. A score of 0-3 is considered functionally independent and a score of 4 to 6 is considered functionally dependent with 6 being death.

Table 20. Modified Rankin Scale (mRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

Source: Broderick, JP, O Adeoye, J Elm, 2017, Evolution of the modified Rankin Scale and Its Use in Future Stroke Trials, Stroke, 48(7)2007-2012.

uw-mRS definition: The uw-mRS is a quality-of-life measure to assess patient perception. It is based on the EQ-5D questionnaire values assigned to the mRS health states.

Efficacy results in extended population (N=474) were consistent with in PEP.

Table 21. Primary Analysis Results for the Primary Endpoint in Extended Population

Response	Andexanet (N=241)	Usual Care (N=233)
Excellent/good	151 (62.7%)	122 (52.4%)
Excellent	136 (56.4%)	106 (45.5%)
Good	15 (6.2%)	16 (6.9%)
Poor/none	90 (37.3%)	111 (47.6%)
Poor/none based on adjudication	78 (32.4%)	106 (45.5%)
Poor/none non-evaluable for administrative reasons	7 (2.9%)	2 (0.9%)
Poor/none non-evaluable for clinical reasons	5 (2.1%)	3 (1.3%)
Difference (96.9% CI)	10.1% (0.5%, 19.7%)	
p-value	0.024	

Source: Adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Tables 14.2.1.1.1a

Table 22. Neurologic Deterioration at 12 and 24 Hours in Extended Population

Timepoint	Andexanet	Usual Care	Andexanet Responders	Usual Care Responders
12 hours	30/225 (13%)	32/220 (15%)	-	-
24 hours	47/154 (31%)	45/152 (30%)	13/94 (14%)	6/76 (8%)

Source: FDA reviewer calculations from ADEFF, ADSL and ADRS datasets

Table 23. Modified Rankin Scale at Baseline and Day 30 in Extended Population

Parameter	Andexanet n/N (%)	Usual Care n/N (%)
mRS 0-3 (baseline)	193/233 (83%)	186/227 (82%)
mRS 0-3 (30 days)	63/225 (28%)	71/222 (32%)
Patients with baseline mRS 0-3	-	-
mRS remained 0-3 at Day 30	57/182 (31%)	66/178 (37%)
mRS change to 4-6 at Day 30	125/182 (69%)	112/178 (63%)
Patients with baseline mRS 4-6	-	-
mRS remained 4-6 at Day 30	32/36 (89%)	36/39 (92%)
mRS change to 0-3 at Day 30	4/36 (11%)	3/39 (8%)

Source: FDA reviewer calculations from ADSL, ADQS datasets.
Abbreviations: mRS, modified Rankin Scale

Table 24. Primary Efficacy Endpoint: Patients Receiving Andexanet vs. Usual Care Based on Planned Andexanet Dose in Extended Population

Planned Andexanet Dose	Andexanet n/N (%)	Usual Care n/N (%)	Difference 96.9% CI	p-value
High (N=103)	22/54 (41%)	22/49 (45%)	-4.9% (-25.8%, 15.9%)	0.61
Low (N=371)	129/187 (69%)	100/184 (54%)	14.6% (3.9%, 25.2%)	0.0035

Source: FDA reviewer calculations from ADEFF and ADSL datasets