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Andexxa

coagulation factor Xa (recombinant), inactivated-zhzo (andexanet)

sBLA 125586/546

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

November 21, 2024

Dr. Christine Knoll & Dr. Karl Kasamon
Medical Officers- Benign Hematology Branch
Division of Clinical Evaluation Hematology
Office of Clinical Evaluation
Office of Therapeutic Products, CBER

Center for Biologics Evaluation and Research
Review Team

Office of Therapeutic Products
Nicole Verdun, MD

Office of Clinical Evaluation
Lola Fashoyin-Aje, MD, MPH

Division of Clinical Evaluation-Hematology
Megha Kaushal, MD
Christine Knoll, MD
Karl Kasamon, MD

Clinical Pharmacology
Sojeong Yi, PhD

Division of Pharmacovigilance
Adamma Mda-Jonas, PhD
Yeowon Kim, PhD

Division of Biostatistics
John Scott, PhD
Lihan Yan, PhD
Lin Huo, PhD
Hairong Shi, PhD

Outline

- Meeting Purpose
- Background on Treatment of Life-Threatening Bleeding Due to Direct Oral Anticoagulants Use
- Andexanet Description and Regulatory History
- Overview of ANNEXA-I Trial Design and Efficacy Results
- ANNEXA-I Safety Review
- Summary
- Discussion Topics

Meeting Purpose

- Discuss and obtain input on the benefit-risk profile of andexanet:
  - Primary endpoint met in confirmatory clinical trial on a composite endpoint consisting of:
    - Brain imaging to assess hematoma expansion
    - NIH Stroke Scale (NIHSS) evaluation of acute clinical outcome
    - Need for rescue medication
  - Treatment effect on andexanet on other clinically meaningful endpoints:
    - Neurologic status at 24 hours
    - Modified Rankin Scale (mRS) at Day 30
    - Overall mortality
  - Increased risk of thrombosis observed with andexanet for the proposed indication in the context of the clinical efficacy shown in ANNEXA-I

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Background - Anticoagulant-Associated Bleeding

- Direct Oral Anticoagulants are the predominant class of anticoagulants
  - Major bleeding occurs in 2% to 4% of patients per year
  - Bleeding is associated with high morbidity & mortality, including intracranial hemorrhage (ICH)

Treatment of Direct Oral Anticoagulant-Associated Major Bleeding

- Treatment of Direct Oral Anticoagulant-associated major bleeding
  - Primary goal of treatment is reversal of anticoagulation
  - Approved reversal agent is andexanet (Accelerated Approval); prothrombin complex concentrates used off-label
- Unmet medical need for treatment remains

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Andexanet (Coagulation Factor Xa (Recombinant), Inactivated-zhzo)

- Product Description:
  - Recombinant variant factor Xa (FXa) that binds to Direct Oral Anticoagulants
  - Modified so that it cannot catalyze the coagulation reaction
- Pro-Coagulant Mechanisms of Action:
  - Binds and sequesters FXa inhibitors → lowers anti-FXa activity (~2 hours)
  - Inactivates tissue factor pathway inhibitor (TFPI) → increases thrombin generation (~96 hours)

Source: Andexxa US. Prescribing Information

Evidentiary Standard for Approval

- Evidentiary Approval Standard
  - Safety and effectiveness demonstrated in adequate and well-controlled trials
- Approval Pathways
  - Traditional Approval
    - Demonstrate effects on symptom, function, and survival
  - Accelerated Approval
    - Improvement over available therapy
    - Effect on surrogate endpoint or intermediate clinical endpoint reasonably likely to predict clinical benefit

Source: FDA Guidance Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products Guidance for Industry (2019);
Section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)); FDA guidance Expedited Programs for Serious Conditions –
Drugs and Biologics (2014)

Andexanet - Regulatory History

- FDA granted Accelerated Approval on May 3, 2018
- Approved Indication:
  - For the treatment of patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding
  - Accelerated Approval granted based on surrogate endpoint of decrease in anti-FXa activity in healthy volunteers
  - A postmarketing requirement (PMR) of a randomized, controlled study was required to verify clinical benefit

Andexanet Post-Marketing Requirement

- Applicant proposed ANNEXA-I as confirmatory trial
  - Protocol submission: April 2018
  - Study initiated: January 2019
  - Protocol revisions: April 2020
  - FDA feedback: October 2020
    - Optimal timing of the primary efficacy endpoint
    - Suggestion to measure clinical outcomes at later timepoints
    - FDA Suggestions not implemented in the protocol
  - sBLA submitted: January 31, 2024

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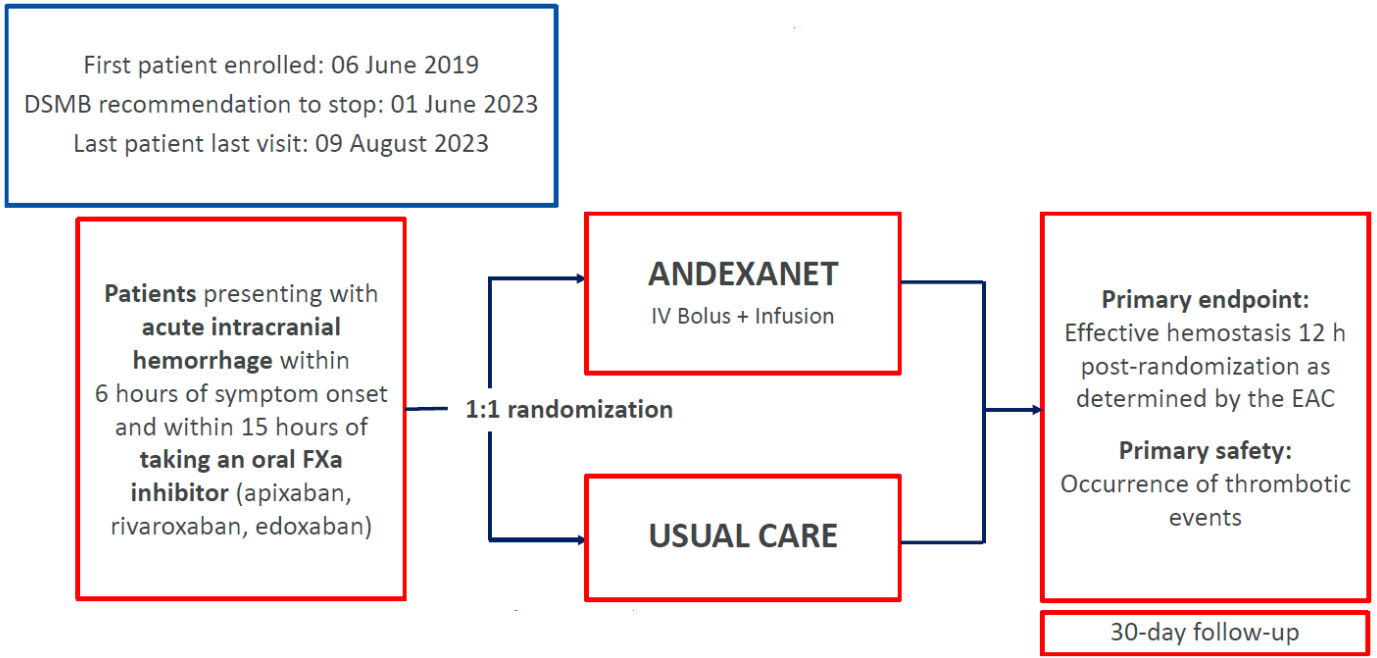
ANNEXA-I Study Design

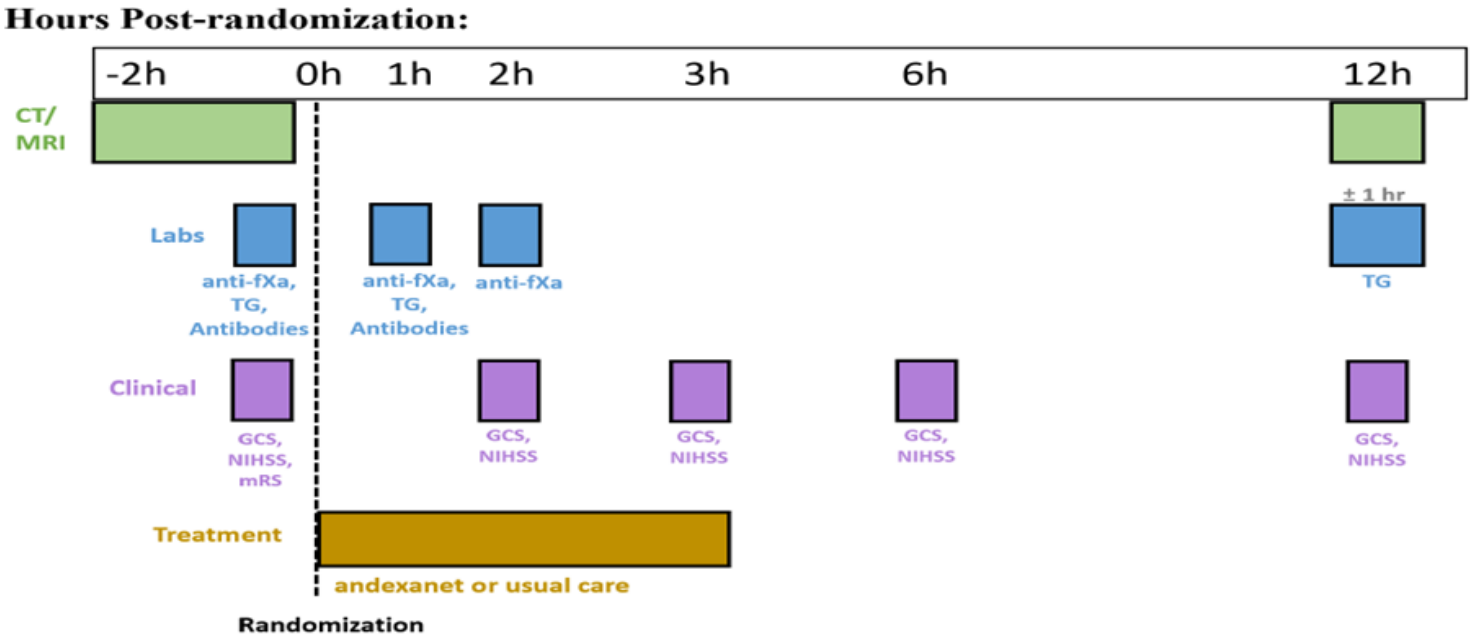


Source: Applicant slide deck application orientation meeting March 7, 2024
Abbreviations: DSMB, Data and Safety Monitoring Board; EAC, endpoint adjudication committee

ANNEXA-I Study Population

- Key eligibility criteria:
  - Acute intracerebral bleed ≥0.5 mL and ≤60 mL
  - Time from bleeding symptom onset to baseline imaging: ≤6 hours
  - CT or MRI within 2 hours of randomization
  - Treatment with rivaroxaban or apixaban:
    - <15 hours prior to randomization or
    - if last dose was >15 hours/unknown and anti-FXa activity >100 ng/mL
  - NIHSS ≤35 and Glasgow Coma Scale (GCS) ≥7
  - No thrombotic event (TE) within last 2 weeks

ANNEXA-I Study Events: 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.

Approved Andexanet Dosing

Andexanet	Initial IV Bolus	Follow-on IV Infusion
Low dose	400 mg	480 mg
High dose	800 mg	960 mg

Source: U.S. Prescribing Information approved May 2018.
Abbreviation: IV, intravenous.

Andexanet Dosing Regimen

FXa Inhibitor Last Dose	Andexanet Dosing Regimen Based on Time Since Last DOAC Dose	
	Less than 8 hours or Unknown	8 hours or more
Rivaroxaban	-	-
≤10 mg	Low dose	Low dose
>10 mg or unknown	High dose	Low dose
Apixaban	-	-
≤5 mg	Low dose	Low dose
>5 mg or unknown	High dose	Low dose

Source: U.S. Prescribing Information.
Abbreviations: DOAC, Direct Oral Anticoagulants; FXa, Factor Xa.

Primary Efficacy Endpoint

- Effective hemostasis 12 hours post-randomization was based on three components:
  - Brain imaging to assess hematoma expansion
  - NIHSS evaluation of acute clinical outcome
  - Need for rescue medication

Primary Efficacy Endpoint

- Effective hemostasis (good/excellent; successful outcome) required the following:
  - **Hematoma volume at 12 hours post-randomization**: Less than 35% increase from baseline (Good: 21% to ≤35%; Excellent: ≤20%)
  - **NIHSS score at 12 hours post-randomization**: Less than 7-point change from baseline
  - **Rescue therapy**: Have not received rescue therapy between 3- and 12-hours post-randomization
    - Any treatment intended to address continued or recurrent bleeding including:
      - blood product besides packed red blood cells or platelets
      - pro-coagulant factor infusions, or systemic hemostatic therapy, besides tranexamic acid
      - unplanned rescue surgical procedure specifically intended to treat the hematoma

Additional Efficacy Endpoints

- Secondary Efficacy Endpoint:
  - Percent change from baseline to nadir in anti-FXa activity during first 2 hours post-randomization
- Select Additional Efficacy Endpoints:
  - Proportion of patients with neurologic deterioration at 24 hours post-randomization
    - NIHSS score increase ≥4 or GCS score decrease of ≥2 compared to baseline
  - Change from baseline in modified Rankin Scale (mRS) score at 30 days post-randomization

ANNEXA-I - Statistical Analysis Plan

- Analysis Plan:
  - Group sequential design: pre-planned interim analysis for efficacy at 50% information (N=450)
  - Lan-DeMets Pocock-type alpha spending: Interim analysis (α=0.0310); Final analysis (α=0.0277)
- Primary Efficacy Analysis:
  - Analysis set: intention-to-treat (ITT)
  - Analysis method: Cochran-Mantel-Haenszel (CMH) method stratified by time from symptom onset to the baseline imaging scan (<180 minutes versus ≥180 minutes)
  - Non-evaluable effective hemostasis status were treated as *poor/none*

ANNEXA-I Efficacy Population

- ANNEXA-I met success criterion at time of pre-planned interim analysis with 50% (~450 of 900) of planned patients
- Interim analysis: Primary efficacy population randomized patients who received apixaban or rivaroxaban (andexanet = 204; Usual Care [UC] = 200)
- Extended population for safety & efficacy sensitivity analyses: andexanet = 241; UC = 233
- Edoxaban (N=45) and enoxaparin (N=3) excluded from FDA analysis – not relevant to the indication

ANNEXA-I Study Conduct - Protocol Deviations

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

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

Results - Demographics & Baseline Characteristics

Parameter	Andexanet (N=204)	Usual Care (N=200)	Total (N=404)
Mean Age (years), n (Range)	78.8 (48, 96)	78.8 (42, 96)	78.8 (42, 96)
Sex (male)	56%	49%	53%
Race (White)	92%	93%	93%
Anticoagulant Apixaban Rivaroxaban	 69 % 31 %	 68% 33%	 68% 32%
Intracerebral bleeding	88%	94%	91%
Hematoma volume (mean)	18.08 mL	16.81 mL	17.45 mL
Reason for anticoagulation Atrial fibrillation	 84%	 83%	 84%

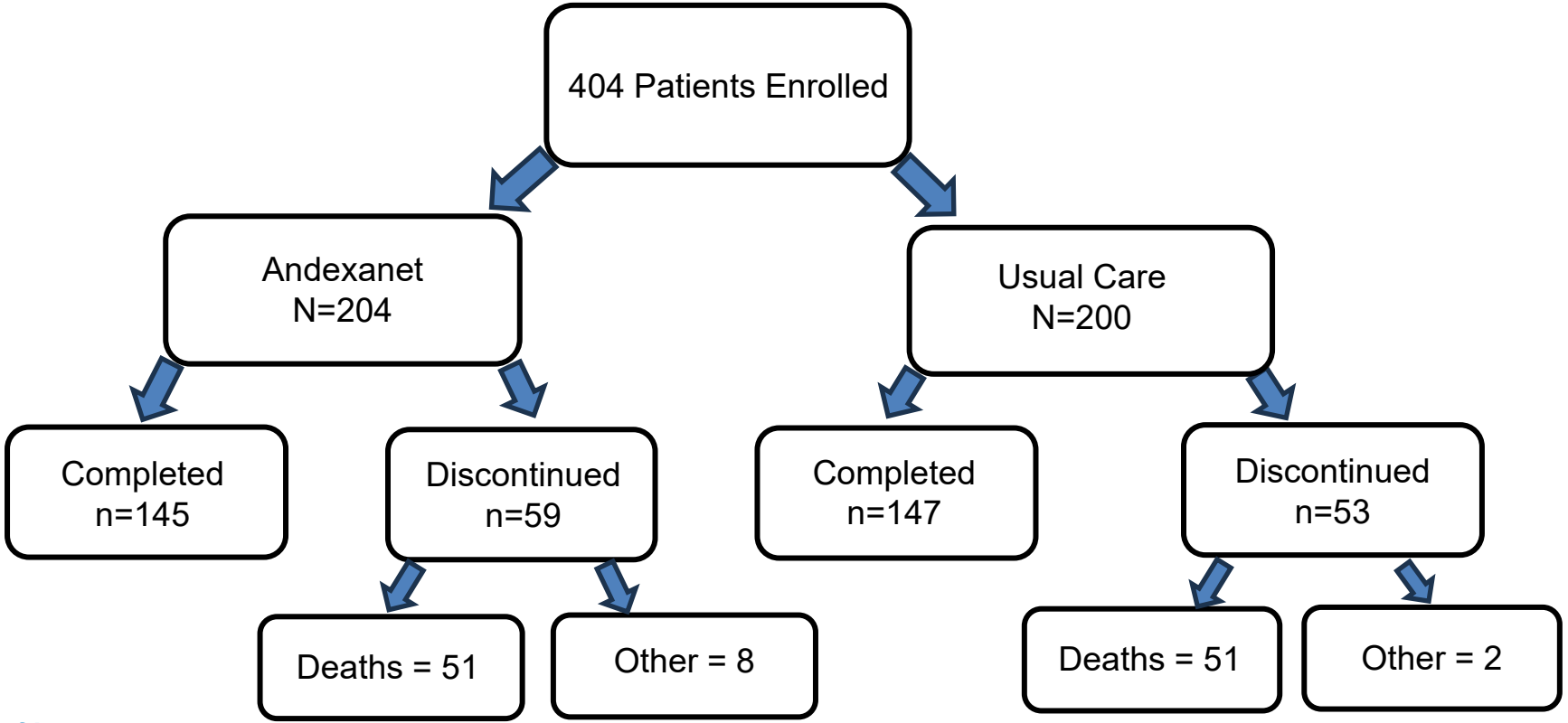
Source: Adapted from - BLA 125586/546; Clinical Study Report 18-513 Edition # 1 CSR Addendum Tables 14.1.1.2a, 14.1.2.1a, 14.1.3.1a, 14.1.3.2a.
Abbreviations: DOAC, Direct Oral Anticoagulants.

Results - Andexanet Dosing

- Mean time to treatment administration post-randomization:
  - Andexanet arm: 25 minutes
  - Usual Care arm: 30 minutes

- Most patients (79%) received low dose andexanet

Results – Patient Disposition



Results - Primary Efficacy Endpoint

Component	Andexanet	Usual Care
Effective hemostasis	134/204 (66%)	106/200 (53%)
Hematoma volume ≤35 increase	150/204 (74%)	119/200 (60%)
NIHSS increase of ≤7 from baseline	170/194 (88%)	159/190 (84%)
No rescue therapy	199/204 (98%)	187/200 (94%)

Δ = 12%
p-value = 0.0113

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
Abbreviations: NIHSS, NIH Stroke Scale.

Primary Efficacy Endpoint Results

Component	Andexanet	Usual Care
Effective hemostasis	134/204 (66%)	106/200 (53%)
Hematoma volume ≤35 increase	150/204 (74%)	119/200 (60%)
NIHSS increase of ≤7 from baseline	170/194 (88%)	159/190 (84%)
No rescue therapy	199/204 (98%)	187/200 (94%)

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
Abbreviations: NIHSS, NIH Stroke Scale.

Secondary Efficacy Endpoint

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

	Andexanet (N=184)	Usual Care (N=176)
Median Anti-FXa activity % change (Range)	-95.0 (-99.1, 1805)	-29.4 (-97.9, 416)

Source: FDA reviewer calculations from ADLB and ADEFF datasets

Secondary Efficacy Endpoint

	Andexanet (N=179)		Usual Care (N=171)	
	Hemostatic Efficacy			
	Responders (N=122)	Non-Responders (N=57)	Responders (N=88)	Non-Responders (N=83)
Median Anti-FXa activity % change (Range)	-95.0 (-99.1, 672)	-95.0 (-98.0, 1805)	-27.8 (-97.9, 416)	-32.2 (-94.4, 128)

Source: FDA reviewer calculations from ADLB and ADEFF datasets

Additional Select Efficacy Endpoints

Parameter	Andexanet	Usual Care
Neurologic deterioration at 24 hours, n (%)	39/124 (32%)	35/121 (29%)
mRS baseline 0-3	N = 151	N = 151
0-3 at day 30, n (%)	48 (32%)	59 (39%)
4-6 at day 30, n (%)	103 (68%)	92 (61%)
mRS baseline 4-6	N = 33	N = 36
4-6 at day 30, n (%)	29 (88%)	33 (92%)
0-3 at day 30, n (%)	4 (12%)	3 (8%)
Mortality at day 30, n (%)	52/204 (26%)	50/200 (26%)

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.
mRS 0-3 = functionally independent; mRS 4-6 = functionally dependent
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

Additional Select Efficacy Endpoints

Parameter	Andexanet Responders	Usual Care Responders
Neurologic deterioration at 24 hours, n (%)	12/77 (16%)	3/60 (5%)
mRS baseline 0-3	N = 100	N = 76
0-3 at day 30, n (%)	41 (41%)	45 (59%)
4-6 at day 30, n (%)	59 (59%)	31 (41%)
mRS baseline 4-6	N = 23	N = 23
4-6 at day 30, n (%)	19 (83%)	20 (87%)
0-3 at day 30, n (%)	4 (17%)	3 (13%)
Mortality at day 30, n (%)	21/134 (16%)	10/106 (9%)

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.
mRS 0-3 = functionally independent; mRS 4-6 = functionally dependent
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

Summary of Efficacy

- ANNEXA-I met the primary endpoint of hemostatic efficacy – andexanet arm (66%) vs. Usual Care arm (53%)
  - Treatment effect most observed on change in hematoma volume at 12 hours
- Secondary efficacy outcome showed that anti-FXa activity % change from baseline was significantly higher in andexanet arm
- Additional efficacy endpoints:
  - Neurologic deterioration at 24 hours and overall mortality with comparable outcomes between the two treatment arms
  - Worse mRS at 30 days in the andexanet treatment arm

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ANNEXA-I Safety Analysis

- Descriptive Analysis
- Analyses were conducted based on the actual treatment the patients received

- Select Safety Endpoints:
  - Incidence of Adverse events
  - Occurrence of thrombotic events through 30 days post-randomization
  - 30-day mortality outcomes (in-hospital, all-cause, and bleeding-related mortality)
  - Hospitalization outcomes (hospitalization length for primary bleeding event, intensive care unit stay, re-hospitalizations)

- Safety Analysis Population
  - Primary efficacy population + patients treated after interim analysis through study end
  - Includes 471 patients: 239 andexanet treated patients and 232 Usual Care

Demographics - Safety Analysis Population

Parameter	Andexanet Treated (N=239)	Usual Care Treated (N=232)
Median age, years Range, years	81 48-96	80 42-96
Male sex, %	54	51
Race/ethnicity, %	-	-
White	94	93
Black/African American	1.7	1.8
Asian	1.3	1.8
Other	3	3.5

Source: FDA reviewer calculations from ADSL dataset

Adverse Events With Incidence Rate ≥5%

Preferred Term/Group Term	Andexanet (N=239) %	Usual Care (N=232) %
Any TEAE	86	82
Urinary tract infection	20	17
Constipation	15	10
Pneumonia	15	14
Pneumonia aspiration	12	9
Headache	9	8
Nausea	9	7
Pyrexia	9	8
Ischemic stroke**	9	1.3
Intracranial hemorrhage*	9	13
Delirium	8	12
Hypertension	8	5
Insomnia	6	3
Vomiting	4	6

Source: Calculated based on ADAE dataset. * Intracranial hemorrhage Group Term includes: Cerebral hematoma, Cerebral hemorrhage, Hemorrhage intracranial, Hemorrhagic stroke, Intracranial hemorrhage, Subarachnoid hemorrhage, Subdural hematoma. ** Ischemic stroke Group Term includes: Cerebellar stroke, Cerebral infarction, Cerebral ischemia, Cerebrovascular accident, Ischemic stroke. Table omits laboratory-only AE of hypokalemia.
Abbreviations: TEAE, treatment-emergent adverse event.

Neurologic Serious Adverse Events, Frequency >1%

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Total number of SAEs (%)	111 (46)	86 (37)
Nervous system disorders	-	-
Ischemic stroke	12 (5)	1 (0.4)
Cerebral hemorrhage	7 (2.9)	11 (4.7)
Hydrocephalus	7 (2.9)	4 (1.7)
Hemorrhage intracranial	6 (2.5)	9 (3.9)
Cerebral hematoma	3 (1.3)	2 (0.9)
Neurologic decompensation	2 (0.8)	7 (3)

Source: reviewer calculations from ADAE dataset.
Abbreviations: TE, thrombotic event.

Non-Neurologic Serious Adverse Events, Frequency >1%

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Total number of SAEs (%)	111 (46)	86 (37)
Cardiac disorders	-	-
Myocardial infarction*	11 (4.6)	2 (0.9)
Cardiac failure	3 (1.3)	0
Infections and infestations	-	-
Pneumonia	11 (4.6)	15 (7)
Pneumonia aspiration	11 (4.6)	7 (3)
Sepsis	6 (2.5)	2 (0.9)
Urinary tract infection	3 (1.3)	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	-	-
Respiratory failure**	6 (2.5)	5 (2.2)
Pulmonary embolism	4 (1.7)	7 (3)

Source: Calculated based on ADAE dataset.
*Group term includes Myocardial infarction, Acute myocardial infarction.
**Group term includes Respiratory failure, Acute respiratory failure.
Abbreviations: TE, thrombotic event.

Adverse Events Leading to Death, Frequency ≥ 1%

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 (2.5)
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 (8)
Cerebral infarction	0	2 (0.9)
Ischemic stroke**	4 (1.7)	0
Respiratory, thoracic, and mediastinal disorders	-	-
Pulmonary embolism	3 (1.3)	1 (0.4)
Respiratory failure	3 (1.3)	4 (1.7)

Source: Calculated based on ADAE dataset. *Group Term Intracranial hemorrhage includes Cerebral hematoma, Cerebral hemorrhage, Hemorrhage intracranial, Hemorrhagic stroke, Intracranial hemorrhage, Subarachnoid hemorrhage, Subdural hematoma. Data presented here are ≥1%, although briefing document lists ≥0.8%.

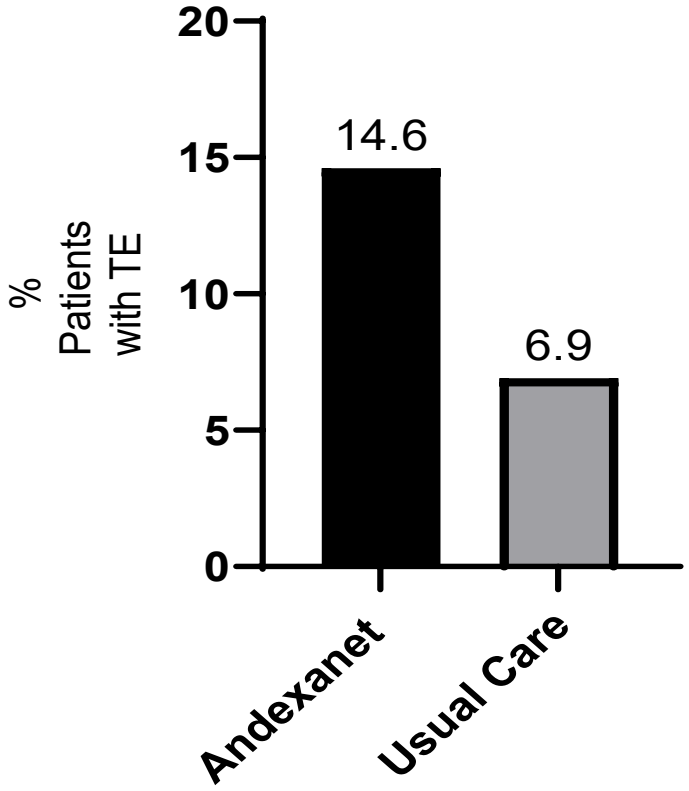
** Group Term Ischemic stroke includes Cerebellar stroke, Cerebral infarction, Cerebral ischemia, Cerebrovascular accident, Ischemic stroke.

Rates of Hospitalization in Andexanet versus Usual Care

	Andexanet (N=239)	Usual Care (N=232)
Number of days hospitalized, median Range	12 1-50	11 1-45
Number of days in intensive care unit, median Range	7 1-30	5 1-40
Patients readmitted, n (%)	6 (2.5)	5 (2.2)

Source: Calculated by reviewer based on ADHO dataset

Patients With Thrombotic Events



Δ= 7.8%

Source: Derived by reviewer from ADAE dataset

FDA-Adjudicated Thrombotic Events

System Organ Class Preferred Term	Andexanet (N=239) n (%)	Usual Care (N=232) n (%)
Total number of TEs	42	18
Ischemic stroke***	14 (6)	1 (0.4)
Myocardial infarction**	11 (4.6)	2 (0.9)
Cerebrovascular accident	4 (1.7)	0
Pulmonary embolism*	4 (1.7)	7 (3)
Sudden cardiac death	0	1 (0.4)
Atrial thrombosis	1 (0.4)	0
Renal infarct	1 (0.4)	0
Cerebellar stroke	1 (0.4)	0
Cerebral ischemia	1 (0.4)	0
Cerebral infarction	1 (0.4)	2 (0.9)
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
Cerebral venous thrombosis	0	1 (0.4)
Troponin increased	0	1 (0.4)
Arterial occlusive disease	0	1 (0.4)

Source: Calculated by reviewer from ADAE dataset.
*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. *** Includes strokes by imaging only, ** Group term includes myocardial infarction and acute myocardial infarction

Timing of Thrombotic Events

Parameter	Andexanet	Usual Care
Patients with Thrombotic Events	N = 35	N = 16
Number of days to TE, median (range)	3.5 (1, 24)	16 (2, 25)
Patients with TE in first 3 days, n (%)	17 (49)	1 (6)
Patients with TE who restarted prophylactic anticoagulant* before TE, n (%)	16 (46)	9 (56)

Source: Reviewer calculations from ADAE and ADCM datasets, FDA information request.
Abbreviations: TE, thrombotic event.
Prophylactic anticoagulant*: receipt of one or more doses of anticoagulant during the follow up period after study treatment completion, before occurrence of the first TE

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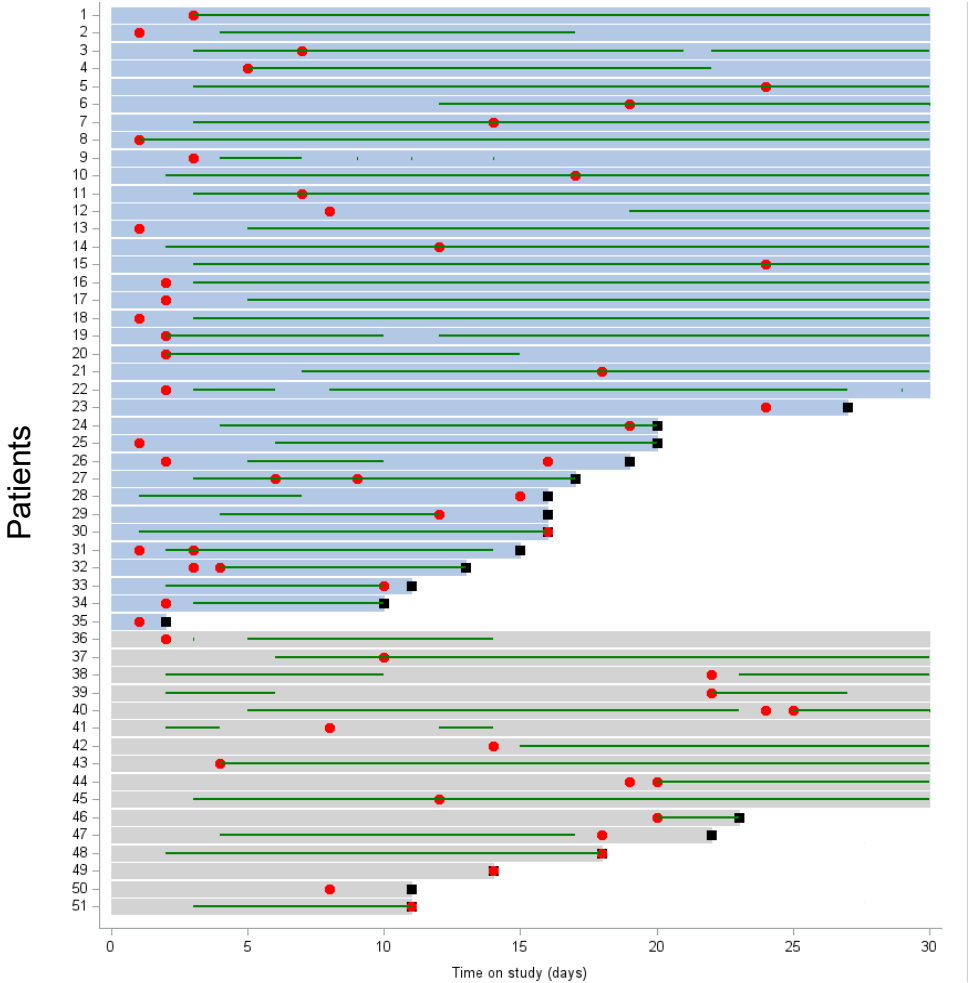
Anticoagulant Use in Patients with TE



Andexanet Patients, n=35

Usual Care Patients, n=16

Thrombotic events

Deaths

Anticoagulation

Source: Calculated based on ADAE, ADCM, ADSL datasets

Anticoagulant Use and Thrombotic Events

Parameter	Andexanet (N=239)	Usual Care (N=232)
Patients who restarted prophylactic anticoagulant*	N = 165	N = 163
Incidence of TE, n (%)	16 (10)	9 (6)
Patients who did not start prophylactic anticoagulant*	N = 74	N = 69
Incidence of TE, n (%)	19 (26)	7 (10)

Source: Reviewer calculations from ADAE and ADCM datasets; FDA information request.
Abbreviations: TE, thrombotic event.
Prophylactic anticoagulant*: receipt of one or more doses of anticoagulant during the follow up period after study treatment completion, before occurrence of the first TE

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Deaths in ANNEXA-I

Deaths From Randomization Until Day 30	Andexanet (N=239)	Usual Care (N=232)
Deaths, n (%)	67 (28)	61 (26)
Deaths from TEs, n (%)	6 (2.5)	2 (0.9)

Source: calculated by reviewer from ADAE dataset
Abbreviations: TE, thrombotic event.

Summary of Safety Results

- TE rate double in andexanet treated patients compared with usual care
- TEs occur much earlier in andexanet treated patients (median 3.5 days vs. median 16 days usual care)
  - Nearly half of TEs occurred in patients who had taken prophylactic anticoagulant
- Deaths from TEs higher in andexanet treated patients compared with usual care

Outline

- Meeting Purpose
- Background on Treatment of Life-Threatening Bleeding Due to Direct Oral Anticoagulants Use
- Andexanet Description and Regulatory History
- Overview of ANNEXA-I Trial Design and Efficacy Results
- ANNEXA-I Safety Review
- Summary
- Discussion Topics

Efficacy Summary - Primary Endpoint

- The study primary efficacy endpoint was met
  - 66% in andexanet arm vs 53% usual care arm

- The largest treatment effect among components of hemostasis was in change in hematoma volume
  - Hematoma volume measurements past 12 hours not submitted
  - Andexanet had smaller positive effects on the other two components - NIHSS and use of rescue therapy

Efficacy Summary – Secondary Endpoint

- Secondary efficacy endpoint - anti-FXa activity % change from baseline greater in andexanet arm compared to usual care arm (-95% vs. -29%)

- No correlation between anti-FXa activity reduction and hemostatic efficacy
  - Anti-FXa activity reduction did not predict clinical benefit

Efficacy Summary- Additional Endpoints

- Outcomes in additional efficacy endpoints between treatment arms (Andexanet vs. Usual Care):
  - Neurological deterioration at 24 hours (31% vs. 29%)
  - Overall mortality (26% vs. 26%)
  - Worse mRS score at 30 days (68% vs. 61%)

Efficacy Summary- Additional Endpoints – cont.

- Among randomized patients who were responders according to primary efficacy endpoint (effective hemostasis at 12 hours):
  - **Neurologic deterioration at 24 hours**: higher in andexanet compared to usual care (16% vs. 5%)
  - **Mortality:** higher in andexanet compared to usual care (16% vs. 9%)
  - **mRS at Day 30**:
    - Smaller proportion of responders in andexanet arm compared to UC arm had stable mRS
      - Patients with baseline mRS 0-3 (41% vs. 59%)
      - Patients with baseline mRS 4-6 (83% vs. 87%)
    - Greater proportion of responders in andexanet arm had a change in mRS at 30 days
      - Patients with baseline mRS 0-3 to 4-6 at 30 days (59% vs. 41%)
      - Patients with baseline mRS 4-6 to 0-3 at 30 days (17% vs. 13%)

Safety Discussion

- TE rate double in andexanet arm compared with usual care arm
- TEs occur much earlier in andexanet arm (median 3.5 days vs. median 16 days usual care)
  - Nearly half of TEs occurred in patients who received prophylactic anticoagulant
- Deaths from TEs higher in andexanet arm compared with usual care

Conclusion

- Decrease in anti-FXa did not predict effects on primary endpoint of hemostasis at 12 hours
- Comparable efficacy
- Thrombosis risk a concern

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Discussion Topics

1. Primary efficacy endpoint in ANNEXA-I was met, with largest treatment affect from among the 3 endpoint components consisting of the change in the hematoma volume at 12 hours. Other clinically meaningful outcomes (e.g., neurologic status at 24 hours and overall mortality) were not different between the two arms; mRS at Day 30 was worse in the andexanet arm. *Discuss whether the treatment effect on the study's primary efficacy endpoint constitutes a clinical benefit to patients.*

   – *Does an effect on hematoma volume change at 12 hours alone constitute clinical benefit?*

   – *Should neurologic status at 24 hours, mRS at Day 30, and overall mortality be incorporated into the assessment of benefit of andexanet?*

   – *Does anti-FXa reduction have a role in the assessment of the benefit of andexanet?*

2. 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 to the usual care. *Are the serious risks of Andexanet as demonstrated in ANNEXA-I acceptable in the indicated population and in the context of the clinical efficacy demonstrated in ANNEXA-I?*


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