Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

CONVERSION TO FULL APPROVAL: ANDEXANET ALFA FOR REVERSAL OF ANTICOAGULATION IN LIFE-THREATENING OR UNCONTROLLED BLEEDING EVENTS IN PATIENTS RECEIVING A DIRECT ORAL FACTOR XA INHIBITOR

ASTRAZENECA
SPONSOR BRIEFING DOCUMENT

CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE

MEETING DATE: 21 NOVEMBER 2024

TABLE OF CONTENTS

Table of Contents 2
List of Tables 6
List of Figures 8
List of Abbreviations 10
1 Executive Summary 11
1.1 Introduction 11
1.2 Patient Unmet Need 12
1.3 Andexanet Mechanism of Action and Dosing 14
1.4 ANNEXA-I 15
1.4.1 Study Design 15
1.4.2 Study Participants 17
1.4.3 Efficacy Results 17
1.4.4 Safety Results 20
1.4.4.1 Overview of Adverse Events 20
1.4.4.2 Mortality Analysis 21
1.4.4.3 Adverse Events of Special Interest 23
1.5 Benefit Risk Conclusions 24
2 Background and Unmet Need 26
2.1 Major Bleeding Events in Patients Receiving Anticoagulation Therapy 26
2.2 Intracranial Hemorrhage 28
2.2.1 Pathology and Epidemiology 28
2.2.2 Prognosis 29
2.2.3 Complications 32
2.3 Current Treatment Options for Anticoagulated Patients Presenting with Major Bleeding 32
2.4 Guidelines for Hemostasis in Major Bleeding Events 33
2.5 Patient Unmet Medical Need 34
3 Product Description 35
3.1 Product Overview 35
3.2 Proposed Indication and Posology 35
3.3 Mechanism of Action 36

4 Regulatory and Development History 38
4.1 Regulatory Milestones 38
4.2 Clinical Development Program 39
5 Studies Supporting Accelerated Approval of Andexanet 41
5.1 ANNEXA-A and ANNEXA-R 41
5.2 ANNEXA-4 43
5.2.1 Study Design 43
5.2.2 Study Participants 44
5.2.3 Efficacy 45
5.2.4 Safety 46
5.2.5 Conclusions 47
6 Clinical Efficacy: Confirmatory Study ANNEXA-I 48
6.1 ANNEXA-I Study Design 48
6.1.1 Overview 48
6.1.2 Treatment 49
6.1.3 Enrollment Criteria 50
6.1.4 Endpoints 50
6.1.4.1 Primary Efficacy Endpoint 50
6.1.4.2 Secondary Efficacy Endpoint 51
6.1.4.3 Additional Efficacy Endpoint 51
6.1.4.4 Safety Endpoints 51
6.1.5 Endpoint Adjudication 51
6.1.6 Statistical Methods 52
6.1.6.1 Sample Size 52
6.1.6.2 Efficacy Analysis Populations 52
6.1.6.3 Endpoint Analyses 52
6.2 ANNEXA-I Patient Population 53
6.2.1 Disposition 53
6.2.2 Treatment Received 54
6.2.2.1 Invasive Intracranial Procedures 54
6.2.3 Baseline Demographics 55
6.2.4 Baseline Characteristics 55

6.3 ANNEXA-I Efficacy Results 58
6.3.1 Primary Endpoint 58
6.3.1.1 Proportion of Patients with Effective Hemostasis 12 Hours Post-Randomization as Determined by the Blinded EAC 58
6.3.1.2 Components of Hemostatic Efficacy 59
6.3.1.3 Subgroup Analyses 60
6.3.2 Secondary Endpoint 62
6.3.2.1 Change in Anti-FXa Activity from Baseline to Nadir at 2 Hours Post-Randomization 62
6.3.3 Additional Endpoints 62
6.3.3.1 Relationship Between Effective Hemostasis and Anti-FXa Activity 62
6.3.4 Sensitivity Analyses – Participants Who Received Apixaban or Rivaroxaban 64
6.3.4.1 Proportion of Patients with Effective Hemostasis 12 Hours Post-Randomization as Determined by the Blinded EAC – Participants Who Received Apixaban or Rivaroxaban 64
6.3.4.2 Change in Anti-FXa Activity from Baseline to Nadir at 2 Hours Post-Randomization – Participants Who Received Apixaban or Rivaroxaban 65
6.4 Efficacy Conclusions 66
7 ANNEXA-I Clinical Safety 67
7.1 Safety Population 67
7.2 Treatment Exposure 67
7.3 Overview of Adverse Events 68
7.4 Common Adverse Events 68
7.5 Serious Adverse Events 69
7.6 Deaths 70
7.6.1 Adjudication 70
7.6.2 AEs Leading to Death 71
7.6.3 All-Cause Mortality Within 30 Days of Randomization 72
7.7 Adverse Event of Special Interest: Thrombotic Events 76
7.7.1 Overview of Thrombotic Events 76
7.7.2 Time to Onset 78

7.7.3 Restarting Anticoagulant Therapy 78
7.7.4 Subgroup Analyses of Adjudicated Thrombotic Events 80
7.8 Immunogenicity 82
7.9 Post-Marketing Safety 83
7.10 Safety Conclusions 83
8 Andexanet Real-World Data 85
8.1 US Multicenter Study: Andexanet vs 4F-PCC (Dobesh et al 2023) 85
8.2 Cohort Study Using Data from the US Department of Veterans Affairs – Andexanet versus 4F-PCC (Sutton et al 2023) 86
8.3 Meta-Analysis Andexanet vs PCC (White et al 2024) 86
8.4 Conclusions 87
9 Benefit-Risk Conclusions 88
10 References 90

List of Tables

Table 1: Comparison of ANNEXA-4 and ANNEXA-I Design Elements 16
Table 2: ANNEXA-I Overview of Adverse Events (Safety Set) 21
Table 3: ANNEXA-I Overview of Deaths (Safety Set) 22
Table 4: ANNEXA-I Overview of Adjudicated Thrombotic Events (Safety Set) 23
Table 5: Interventions to Reverse Anticoagulation Therapy 33
Table 6: Andexanet Dose Based on Rivaroxaban or Apixaban Dose 36
Table 7: Summary of Pharmacokinetic Parameters with High and Low Dose Andexanet 37
Table 8: Key Interactions between AstraZeneca and FDA on ANNEXA-I 38
Table 9: ANNEXA-4 Patient Demographics and Baseline Characteristics 44
Table 10: ANNEXA-4 Patient Medical History (Safety Population) 44
Table 11: ANNEXA-4 Adverse Event Overview (Safety Population) 47
Table 12: Adjudicated Thrombotic Events within Day 30 (Safety Population) 47
Table 13: ANNEXA-I Patient Disposition 53
Table 14: ANNEXA-I Time to Treatment (ITT Set, Primary Efficacy Population) 54
Table 15: ANNEXA-I Demographic Characteristics (ITT Set, Primary Efficacy Population) 55
Table 16: ANNEXA-I Baseline Characteristics (ITT Set, Primary Efficacy Population) 56
Table 17: ANNEXA-I Baseline Characteristics of Initial Bleed Event (ITT Set, Primary Efficacy Population) 57
Table 18: Medical History (Safety Set, Primary Efficacy Population) 58
Table 19: Relationship between Effective Hemostasis with Anti-FXa Activity (ITT Set, Primary Efficacy Population) 63
Table 20: Association between Effective Hemostasis and Reduction in Anti-FXa Activity, Baseline Anti-FXa Activity, Hematoma Volume, Diastolic Blood Pressure, and Time from Symptom Onset to Treatment (ITT Set, Extended Population) 64
Table 21: Overview of Adverse Events (Safety Set) 68
Table 22: Adverse Events with Incidence Rate ≥ 5% (Safety Set) 69
Table 23: Serious Adverse Events with Incidence Rate ≥ 1% (Safety Set) 70

Table 24: Treatment-Emergent Adverse Events Leading to Death, Frequency ≥ 2 Patients in Either Treatment Group (Safety Set)..... 72
Table 25: Summary of Deaths by Cause Based on Adjudication (Safety Set)..... 73
Table 26: Mortality Rate by Dose Eligibility and Baseline Characteristics (Safety Set) 76
Table 27: Overview of Adjudicated Thrombotic Events (Safety Set)..... 77
Table 28: Adjudicated Thrombotic Events Leading to Death (Safety Set) 78
Table 29: Time of Onset of First Thrombotic Event (Safety Set)..... 78
Table 30: Difference in Proportion of Patients with Adjudicated Thrombotic Events up to Day 30, Post Hoc Analysis Based on Medical History (Safety Set) 82
Table 31: ANNEXA-I Immunogenicity Results..... 82
Table 32: In-Hospital Mortality Andexanet vs 4F-PCC..... 86

List of Figures

Figure 1: Studies Supporting Accelerated and Full Approval of Andexanet 12
Figure 2: Andexanet Anti-FXa Activity in ANNEXA-A and ANNEXA-R 15
Figure 3: ANNEXA-I Primary Efficacy Results: Hemostatic Efficacy (Primary Efficacy Population) 18
Figure 4: ANNEXA-I Comparison of Patients Not Achieving Primary Endpoint Components (Primary Efficacy Population) 19
Figure 5: Line Plot of Anti-FXa Activity by Treatment in Patients Overall (ITT Set, Primary Efficacy Population) 20
Figure 6: Kaplan Meier Plot of 30-Day All-Cause Mortality (Safety Set) 22
Figure 7: Estimated Number of Patients in the US Taking Oral FXa Inhibitors over Time (2018 – 2022) 27
Figure 8: Estimated Number of Patients on FXa Inhibitors Admitted to Hospital in the United States (2015 – 2019) 28
Figure 9: Poor Outcomes Associated with Hematoma Expansion 30
Figure 10: Mortality Rates in Patients Receiving FXa Inhibitors – RWE Studies and Clinical Trials 30
Figure 11: In-Hospital Mortality Rates in Patients with FXa Inhibitor-Related Gastrointestinal Bleeds 31
Figure 12: Andexanet Mechanism of Action 36
Figure 13: Andexanet Anti-FXa Activity in ANNEXA-A and ANNEXA-R 42
Figure 14: ANNEXA-4 Study Design 43
Figure 15: ANNEXA-4 Co-Primary Efficacy Results (Efficacy Population) 45
Figure 16: ANNEXA-4 Hemostatic Efficacy (Efficacy Population) 46
Figure 17: Annexa-I Study Design 49
Figure 18: ANNEXA-I Primary Efficacy Results: Hemostatic Efficacy (ITT Set, Primary Efficacy Population) 59
Figure 19: ANNEXA-I Primary Efficacy Results by Component (ITT Set, Primary Efficacy Population) 60
Figure 20: ANNEXA-I Primary Endpoint Key Prespecified Subgroup Analyses (ITT Set, Primary Efficacy Population) 61
Figure 21: ANNEXA-I Primary Endpoint Subgroup Analyses by Dose Eligibility (ITT Set, Primary Efficacy Population) 61

Figure 22: Percent Change from Baseline in Anti-FXa Activity by Treatment in Patients Overall (ITT Set, Primary Efficacy Population)..... 62

Figure 23: ANNEXA-I Hemostatic Efficacy at 12 Hours in Patients Receiving Apixaban and Rivaroxaban (ITT Set, Primary Efficacy Population)..... 65

Figure 24: Percent Change in Anti-FXa Activity from Baseline to 2 Hours Post-Randomization in Participants Who Received Apixaban or Rivaroxaban (ITT Set, Primary Efficacy Population)..... 66

Figure 25: Kaplan-Meier Plot of All-Cause Mortality (Safety Set)..... 74

Figure 26: Mortality by Increasing Sample Size (Safety Set)..... 75

Figure 27: Thrombotic Events in Patients with/without Re-Anticoagulation in the Follow-up Period (Safety Set)..... 79

Figure 28: Re-Anticoagulation Swim Lane Plot for Patients Experiencing a Thrombotic Event (Safety Set)..... 80

Figure 29: Forest Plot of Difference in Proportion of Patients with Adjudicated Thrombotic Events (Safety Set)..... 81

List of Abbreviations

Abbreviation	Definition
4F-PCC	Four-factor prothrombin complex concentrate
AE(s)	Adverse event(s)
CT	Computed tomography
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
FDA	Food and Drug Administration
FXa	Activated factor X
GCS	Glasgow Coma Scale
GI	Gastrointestinal
HR	Hazard ratio
ICrH	Intracranial hemorrhage
ITT	Intent to treat
IV	Intravenous
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
OAC	Oral anticoagulation
OR	Odds ratio
ORANGE	Oral Anticoagulant Agent-Associated Bleeding Events Reporting System
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic
PK	Pharmacokinetic
PMR	Post-marketing requirement
rFVIIa	Recombinant activated factor VII
RWE	Real-World Evidence
SAE(s)	Serious adverse event(s)
sBLA	Supplemental Biologics License Application
TEAE(s)	Treatment emergent adverse event(s)
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
US	United States
USPI	United States Prescribing Information

1 EXECUTIVE SUMMARY

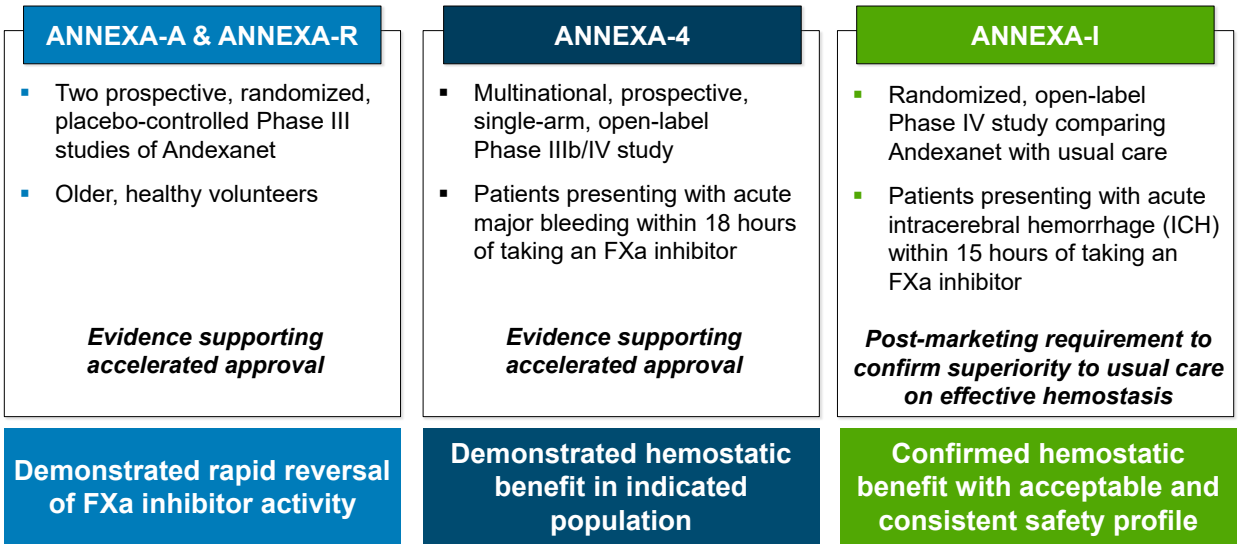
1.1 Introduction

Patients receiving direct oral activated factor X (FXa) inhibitors who experience an acute major bleeding event are at a high risk of mortality and morbidity. These patients need fast-acting, targeted therapies that rapidly restore physiologic coagulation by effectively reversing the anticoagulant effects of FXa inhibitors. In these emergency situations, physicians rely on rapid and specific interventions to manage the patients' immediate risk of death from the life-threatening bleeding event. Andexanet alfa (ANDEXXA® [coagulation factor Xa (recombinant), inactivated-zhzo]), hereafter referred to as andexanet, is an effective and safe specific antidote that rapidly reverses the anticoagulation effects of direct FXa inhibitors, restores hemostasis, and is an important part of the care bundle needed to stop the bleeding in patients who experience life-threatening or uncontrolled bleeding in emergency situations.

Andexanet was granted breakthrough designation (November 2013), Orphan drug designation (February 2015), and Accelerated Approval by the Food and Drug Administration (FDA) in May 2018 based on clinical evidence demonstrating rapid and potent reversal of FXa inhibition in healthy volunteers and preliminary data in patients experiencing life-threatening or uncontrolled bleeding (Figure 1). As a condition of Accelerated Approval, a post-marketing requirement (PMR) was issued to verify the hemostatic effect of andexanet as described in the May 2018 Approval letter (https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm).

To address this PMR, a Phase 4 study, ANNEXA-I (Study 18-513), was designed in collaboration with the FDA and undertaken to provide confirmatory evidence of hemostasis to confer traditional approval of andexanet and verify the clinical benefit.

Figure 1: Studies Supporting Accelerated and Full Approval of Andexanet



FXa: activated factor X.

Evidence from the first randomized, controlled study, ANNEXA-I, demonstrates that andexanet provides superior hemostatic efficacy compared to usual care in patients with a life-threatening or uncontrolled bleeding event after receiving a direct oral FXa inhibitor. The final results from the ANNEXA-I trial are both statistically significant and clinically meaningful and confirmed andexanet's ability to rapidly reverse the anticoagulation effects of FXa inhibitors (Connolly et al 2024). The supplemental Biologics License Application (sBLA) for full approval of andexanet was submitted in January 2024 with results from ANNEXA-I.

While early thrombotic events are a known risk described in andexanet's label, they are manageable within the comprehensive acute care setting, where critical care teams are fully equipped to address these complications, and re-initiation of anticoagulation therapy is recommended once the patient is stabilized to prevent future events. Safety data from ANNEXA-I and ANNEXA-4 support an acceptable and consistent safety profile of andexanet in the setting of uncontrolled and life-threatening bleeding events. Based on the totality of evidence from clinical trials and post-marketing experience, no new safety signals have been identified.

As described in this briefing document, overall, the efficacy and safety results of the ANNEXA-I trial support the conversion to traditional approval of the currently approved indication and posology for andexanet.

1.2 Patient Unmet Need

FXa inhibitors have become the new standard of care for anticoagulation in many clinical situations, including atrial fibrillation and venous thromboembolism. Globally in

2024, approximately 25 million patients will receive FXa inhibitors, and in 2022, approximately 4.8 million patients in the United States (US) received FXa inhibitors to prevent harmful blood clots from forming(Centers for Medicare and Medicaid Services 2022). However, these agents increase the risk of an acute major bleeding event. Since FXa inhibitors inhibit natural coagulation, it can be difficult to stop the bleeding.

As the use of FXa inhibitors increases, so does the number of hospital admissions for bleeding events linked to these medications. Studies show that per year, 3% to 5% of patients on FXa inhibitors experience life-threatening or uncontrolled bleeding requiring hospitalization (Crawley and Anderson 2020). In 2019 alone, approximately 190,000 patients were hospitalized in the US with an FXa inhibitor related major bleeding event. Alarmingly, this rate has more than doubled from 2015 - 2019 in the US (Truven Health Analytics 2019).

Major bleeding events associated with FXa inhibitors can occur across various body sites and all have been shown to manifest as acute major bleeds leading to hospitalization. A multicenter retrospective survey from 2016 to 2019 highlighted gastrointestinal (GI), intracranial hemorrhage (ICrH), and trauma-related bleeds as the leading causes of hospitalizations (Coleman et al 2021).

Patients on FXa inhibitors who present with severe, uncontrolled bleeding face life-threatening risks. In these critical situations, emergency physicians use a multi-faceted bundle of care that integrates fast-acting, effective therapies including blood pressure control, surgical intervention, and anticoagulant reversal to manage the patient’s immediate risk of death.

In cases of ICrH, rapid intervention to control the bleeding is critical, as hematoma expansion is a well-known predictor of poor clinical outcomes. As the skull is a confined compartment, even a small hematoma expansion in the brain can be clinically significant. Each 1 mL increase in hematoma volume is associated with a 5% rise in the likelihood of death or severe disability (Delcourt et al 2012). Therefore, in the setting of ICrH, limiting hematoma expansion is a goal of therapeutic intervention.

FXa inhibitor-related GI bleeds are also linked to significant in-hospital mortality, further highlighting the need for specific, fast-acting therapies to manage these life-threatening bleeding events. Multiple studies have evaluated the relationship between FXa inhibitor related GI bleeds and in-hospital mortality and reported rates ranging from 1.6% to 7% (Coleman et al 2021; Milling et al 2018; Pannach et al 2017; Singer et al 2017). These studies support the need for quick intervention and highlight the importance of FXa specific reversal agents in restoring physiologic coagulation in all types of uncontrolled and life-threatening bleed events.

While reversing the effects of the FXa inhibitor effectively restores the body’s ability to clot, it also reintroduces the patient to their baseline risk of thrombotic events. In addition, the pathophysiology of major hemorrhage, especially associated with trauma, may predispose the patient to a prothrombotic state of coagulation that would be

considered additive with their underlying thrombotic risk factors (ie, the risk of a thrombotic event is heightened by the bleeding event itself) (Moore et al 2021). The subsequent hospitalization and its complications also increase the risk of thrombotic events in patients experiencing acute major bleeding events.

In emergency settings, the immediate priority is to stop the bleed and rapidly stabilize the patient as failure to do so may result in death. Multiple studies highlight the importance of a bundle of care approach in managing patients with uncontrolled, life-threatening bleeding. In these situations where time is crucial, care teams implement a multi-pronged strategy of targeted, individualized treatments with the goal of minimizing the patient's immediate risk of death.

Andexanet is the only approved targeted approach that has been shown to reverse the anticoagulant effects of apixaban and rivaroxaban, addressing a medical need for specific reversal agents. As such, multiple national and international guidelines have supported the use of specific reversal agents for life-threatening bleeding related to FXa inhibitors (Christensen et al 2019; Greenberg et al 2022).

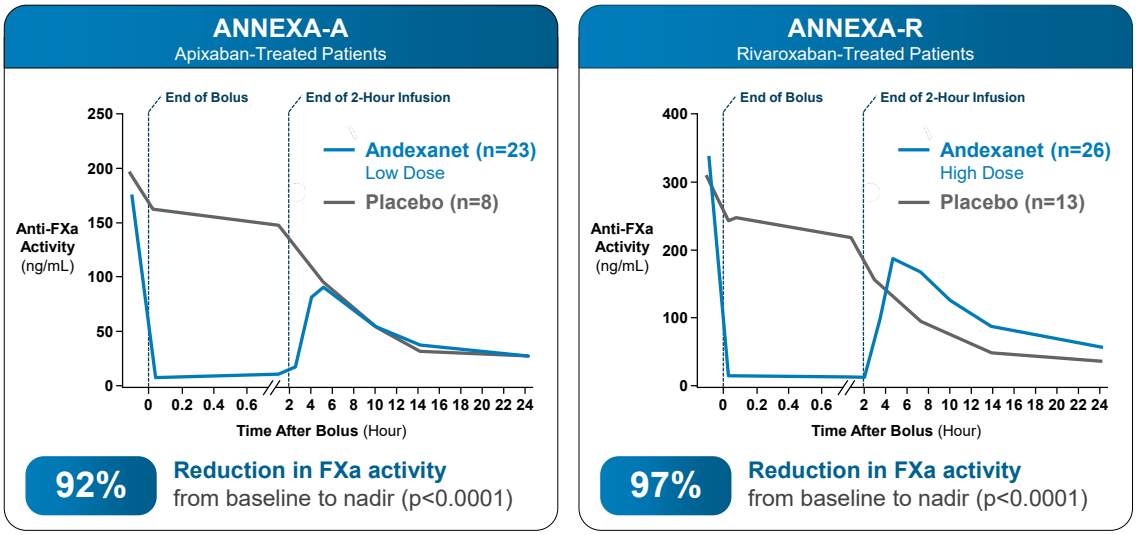
Therapies such as 4-factor prothrombin complex concentrate (4F-PCC), which are known to have a slower onset of effect, are commonly used off-label in this clinical setting.

Andexanet is a vital component of the bundle of care used by emergency physicians to rapidly reverse FXa inhibitors, restore physiologic coagulation and manage uncontrolled, life-threatening bleeding events.

1.3 Andexanet Mechanism of Action and Dosing

Andexanet exerts its procoagulant effect by binding and sequestering the FXa inhibitors, including rivaroxaban and apixaban. Another observed procoagulant effect of the andexanet protein is its ability to bind to, and inhibit the activity of, tissue factor pathway inhibitor (TFPI). Inhibition of TFPI activity can increase tissue factor (TF)-initiated thrombin generation. Data from ANNEXA-A and ANNEXA-R showed that andexanet reversed the anticoagulant activity of apixaban and rivaroxaban in older healthy participants within minutes after administration and for the duration of infusion (Figure 2).

Figure 2: Andexanet Anti-FXa Activity in ANNEXA-A and ANNEXA-R



Low Dose = 400-mg bolus + 480 mg × 2-hr infusion; High Dose = 800-mg bolus + 960 mg × 2-hr infusion; Placebo = bolus + 2-hr infusion

Andexanet reverses the anticoagulant exacerbating effects on bleeding but does not repair bleeding lesions and is not intended to reverse damage caused by the index bleeding event or directly improve post-bleeding recovery.

To completely reverse anti-FXa activity, andexanet molar concentration must exceed the FXa inhibitor concentration. The recommended dosing of andexanet is therefore based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor, as described in Table 6:

- Low dose: 400 mg intravenous (IV) bolus, followed by a continuous infusion of 480 mg at 4 mg/min for approximately 120 minutes
- High dose: 800 mg IV bolus, followed by a continuous infusion of 960 mg at 8 mg/min for approximately 120 minutes

1.4 ANNEXA-I

1.4.1 Study Design

ANNEXA-I was the first randomized, open-label, multicenter, Phase 4 study designed to evaluate the use of andexanet in patients receiving direct oral FXa inhibitors presenting with an acute intracranial bleeding episode. ANNEXA-I was designed as a post-marketing requirement study to test the hypothesis that andexanet is superior to usual care in effective hemostasis at 12 hours post-randomization. Notably, the study design of ANNEXA-I was based on learnings from ANNEXA-4, which demonstrate that andexanet is an effective reversal agent for FXa inhibitors. Unlike ANNEXA-4, which

evaluated all bleed types, ANNEXA-I specifically focused on intracerebral hemorrhage events to allow for an objective measure of hemostatic efficacy using established methods for measuring hematoma size and expansion (Table 1). Thus, ANNEXA-I is a reversal study to verify the control and stop of bleeding.

Table 1: Comparison of ANNEXA-4 and ANNEXA-I Design Elements

	ANNEXA-4	ANNEXA-I
Design	Single-arm	Randomized-controlled vs usual care including PCCs and no hemostatic treatment
Goal	Demonstrate Hemostatic Benefit in Patients with FXa-Inhibitor Related Major Bleed	Confirm Hemostatic Benefit Compared to Usual Care
Bleed Type	All Bleed Types	Intracranial Hemorrhage Established methods for measuring hematoma size and expansion provide objective assessment of hemostatic efficacy

FXa: activated factor X; PCC: prothrombin complex concentrate.

To support global development and align with the approved indications of andexanet throughout the world, ANNEXA-I enrolled patients receiving apixaban, rivaroxaban, and edoxaban. To align with the current US Prescribing Information (USPI), this briefing document includes the results from both the prespecified primary analysis population including all patients regardless of FXa inhibitor as well as sensitivity analyses focusing on the subset of patients receiving apixaban or rivaroxaban.

Eligible patients were randomized 1:1 to andexanet or usual care, stratified by the site's intended-usual-care-agent response and also the time from symptom onset to baseline scan. Imaging evaluations were performed at baseline and approximately 12 hours following randomization. Neurologic assessments were conducted at baseline, 2, 3, 6, 12, 24, and 72 hours after randomization.

The primary efficacy endpoint in ANNEXA-I was effective hemostasis 12 hours post-randomization. Effective hemostasis was defined by meeting all 3 of the following criteria:

1. Hematoma volume: ≤ 35% increase in hematoma volume compared with baseline on repeat computed tomography (CT) scan or magnetic resonance imaging (MRI) at 12 hours as determined by a blinded Endpoint Adjudication Committee (EAC)
2. National Institutes of Health Stroke Scale (NIHSS): ≤ 6-point change from baseline at 12 hours

3. Rescue therapy administration: None used between 3- and 12-hours post-randomization

The secondary efficacy endpoint in ANNEXA-I was percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization.

ANNEXA-I included an interim analysis after 50% of the estimated total sample size of 900 patients were adjudicated for the primary hemostasis outcome. Based on the prespecified interim analysis, the independent Data Safety Monitoring Board (DSMB) recommended that the study be stopped. Therefore, the study was stopped early, and efficacy endpoints were analyzed in the Primary Efficacy Population (N=452), which includes all randomized patients included in the interim analysis; analyses were also performed in the full Extended Population, which included all randomized patients (N=530). Safety was analyzed in the Safety Population (N=527), which includes all patients who participated in the study and received randomized treatment.

1.4.2 Study Participants

The primary efficacy population included 224 patients randomized to receive andexanet and 228 in the usual care group. More than 70% of patients in both groups completed the study. The primary reason for discontinuation from the study was patient death (25.0% in the andexanet group and 25.9% in the usual care group; see Table 13). No patients were lost to follow-up.

In the andexanet group, based on the approved posology, 78.1% of patients received the low-dose regimen and 20.1% of patients received the high-dose regimen (1.8% were randomized to andexanet but were not treated with andexanet). In the usual care group, 84.6% of patients were treated with a prothrombin complex concentrate (PCC), 15.4% of patients did not receive PCCs.

1.4.3 Efficacy Results

ANNEXA-I demonstrated that andexanet is superior to usual care in achieving effective hemostasis at 12 hours post-randomization, in patients presenting with an acute ICrH who were receiving a direct oral FXa inhibitor.

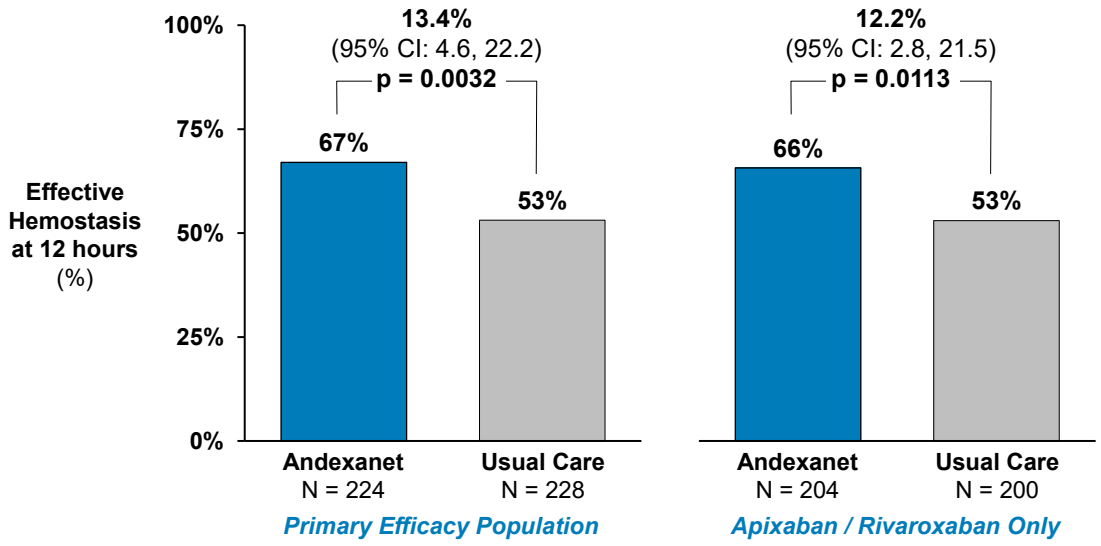
In the Primary Efficacy Population, a total of 67.0% of patients in the andexanet group compared to 53.1% of patients in the usual care group achieved the primary endpoint, resulting in a statistically significant adjusted absolute treatment difference of 13.4% (p=0.003; Figure 3).

Sensitivity analyses of the primary endpoint, including the post hoc analysis requested by the FDA to analyze only patients who received the FXa inhibitors apixaban or rivaroxaban, consistently demonstrated a meaningful benefit of andexanet compared to usual care (see Section 6.3.4).

In the subset of patients who were receiving apixaban and rivaroxaban, a consistent hemostatic benefit favoring andexanet was observed compared to usual care, 66% vs

53% respectively (p=0.0113). These results support the robustness of the primary efficacy findings.

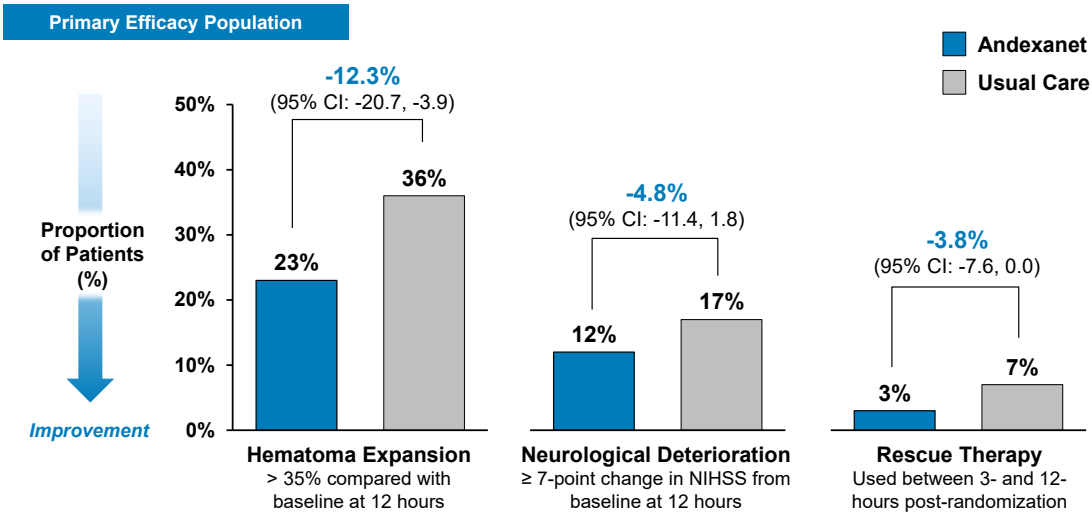
Figure 3: ANNEXA-I Primary Efficacy Results: Hemostatic Efficacy (Primary Efficacy Population)



CI: confidence interval.
Note: The p-values, proportion differences and 95% CIs are from Cochran-Mantel Haenszel test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

In addition, the treatment effect was generally consistent across pre-defined subgroups based on demographic and important baseline characteristics, with no treatment by subgroup interaction p-values < 0.05 (see Figure 20). Furthermore, numerical improvements in the andexanet group compared to the usual care group were observed for each of the 3 components assessed in the primary endpoint (Figure 4).

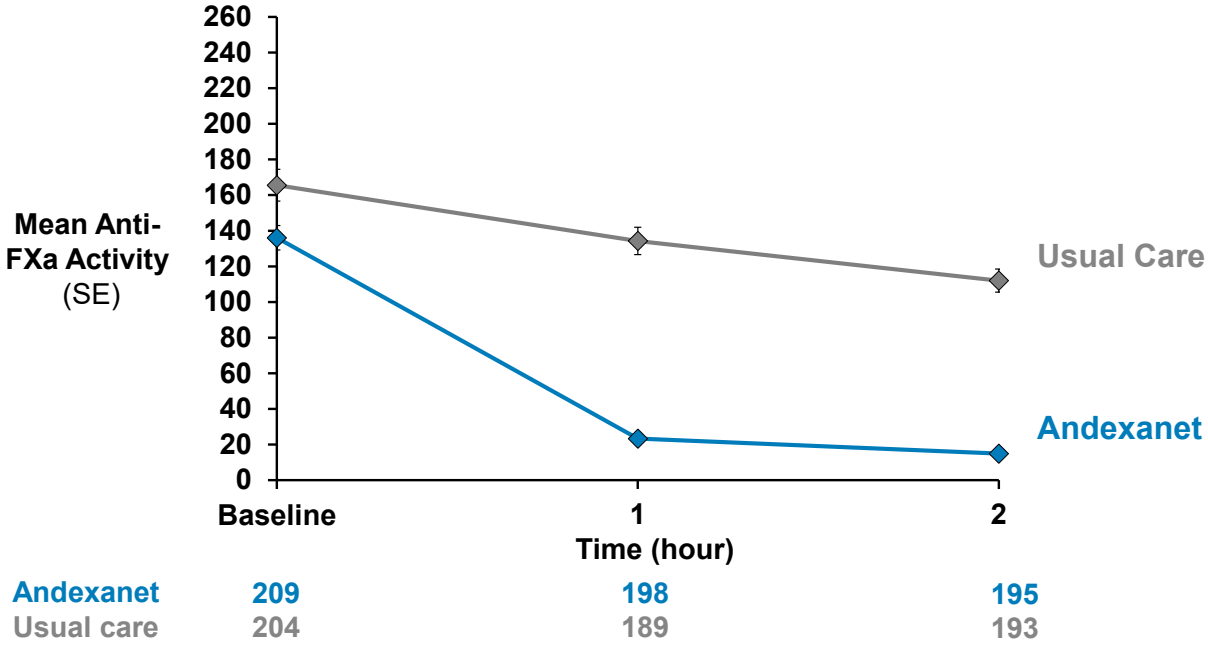
Figure 4: ANNEXA-I Comparison of Patients Not Achieving Primary Endpoint Components (Primary Efficacy Population)



CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale.

Andexanet was superior to usual care in reducing anti-FXa activity from baseline to nadir during the first 2 hours post-randomization, with a 94% median reduction in the andexanet group compared to a 27% median reduction in the usual care group ($p<0.0001$ see Figure 22). ANNEXA-I reductions in anti-FXa activity were consistent with results from ANNEXA-A and ANNEXA-R, which showed a 92% reduction within 2 minutes. This corresponds to actual values of anti-FXa activity which are well below 30 ng/mL in the andexanet group, while in the usual care group patients could be considered still anticoagulated by their anti-FXa inhibitor at an anti-FXa activity >100 ng/mL (Figure 5).

Figure 5: Line Plot of Anti-FXa Activity by Treatment in Patients Overall (ITT Set, Primary Efficacy Population)



FXa: activated factor X.

1.4.4 Safety Results

Andexanet has a well-established safety profile based on multiple studies including 553 healthy volunteers and 741 patients in the setting of life-threatening or uncontrolled bleeding and post-marketing use. As of 31 July 2024, cumulative global post-marketing exposure of andexanet is approximately 64,370 patients, and no new safety signals have been identified in post-marketing surveillance.

1.4.4.1 Overview of Adverse Events

The safety population from ANNEXA-I includes a total of 527 randomized patients, 262 in the andexanet group and 265 in the usual care group. Overall, most patients in both study groups experienced a treatment-emergent adverse event (TEAE; Table 2). While the majority of AEs were mild-to-moderate in severity, more patients in the andexanet group than in the usual care group experienced severe TEAEs, serious TEAEs (TESAEs), and TEAEs leading to death. No new safety signals were detected.

The overall safety profile of andexanet compared to usual care was similar in the subset of patients receiving apixaban and rivaroxaban. Given the similarities between populations, and to provide the most robust assessment of andexanet safety, the safety discussion will focus on the totality of the evidence from the overall population.

Table 2: ANNEXA-I Overview of Adverse Events (Safety Set)

	Primary Safety Population		Apixaban and Rivaroxaban Safety Population	
Patients, n (%)	**Andexanet (N=262)**	**Usual Care (N=265)**	**Andexanet (N=239)**	**Usual Care (N=232)**
TEAE	223 (85.1)	219 (82.6)	205 (85.8)	190 (81.9)
TESAE	120 (45.8)	96 (36.2)	111 (46.4)	86 (37.1)
TEAE leading to withdrawal of study drug	0	0	0	0
TEAE leading to interruption of study drug	1 (0.4)	0	1 (0.4)	0
TEAE leading to death	64 (24.4)	54 (20.4)	59 (24.7)	49 (21.1)
All-cause mortality through 30 days	74 (28.2)	70 (26.4)	67 (28.0)	61 (26.3)

TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.
Note: In accordance with the study protocol, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurred within the first 12 hours post-randomization were not regarded as an AE or SAE except when there was evidence suggesting a causal relationship between the drug and the event. Thus, death due to disease progression was not reported with an SAE or AE leading to death.

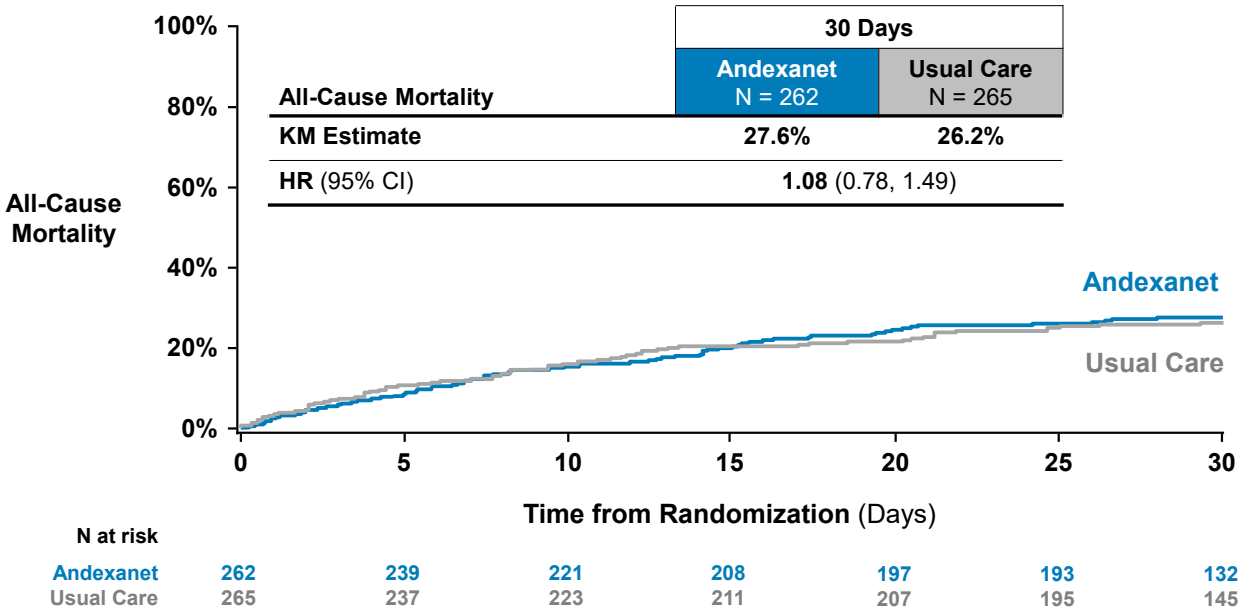
Overall, TEAEs by preferred term were reported at similar rates between treatment groups. The most frequently reported TEAEs in both groups were urinary tract infection, pneumonia, and hypokalemia (see Table 22). The 2 primary drivers of SAEs in both treatment groups were infections such as pneumonia, pneumonia aspiration, and sepsis and SAEs due to the underlying index bleeding event (see Table 23). Cerebral hemorrhage, ICrH, infections including pneumonia, aspiration pneumonia, and sepsis were the leading causes of death (see Table 24). These event rates are well in line with what has been previously described in patients with ICrH and related complications, including infections, developed during hospital admission.

In ANNEXA-I, there were 144 deaths (74 deaths in the andexanet group and 70 deaths in the usual care group). In total, 26 out of the 144 deaths did not have TEAEs reported since they were considered as deaths due to disease progression (10 deaths in the andexanet group and 16 deaths in the usual care group). In accordance with the protocol, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurred within the first 12 hours post-randomization was not to be regarded as an AE or SAE except when there was evidence suggesting a causal relationship between the drug and the event.

1.4.4.2 Mortality Analysis

An analysis of mortality rates within 30 days of randomization revealed similar rates in the treatment groups. The 30-day Kaplan-Meier estimates were 27.6% in the andexanet group and 26.2% in usual care, with the 2 curves crossing at various timepoints (Figure 6).

Figure 6: Kaplan Meier Plot of 30-Day All-Cause Mortality (Safety Set)



CI: confidence interval; HR: hazard ratio; KM: Kaplan-Meier.

All events of death through 30 days were adjudicated to be cardiovascular (CV)-related except for one patient in the usual care group. As per the adjudication charter, all intrahospital deaths following the presenting ICrH with no other apparent cause were adjudicated as CV-related. Bleeding-related deaths occurred in 14 andexanet treated patients (5.3%) and 19 patients in the usual care group (7.2%; Table 3). A bleeding-related death was defined as a death within 72 hours of randomization and not associated with the occurrence of an identified thrombotic event. The acute phase of ICrH is a well recognized 72-hour window that is a period of extreme risk for mortality in these vulnerable hospitalized patients. In-hospital mortality was similar between groups. Additional details are provided in Section 7.6.3.

Table 3: ANNEXA-I Overview of Deaths (Safety Set)

Deaths, n (%)	Andexanet (N=262)	Usual Care (N=265)
30-day all-cause mortality	74 (28.2)	70 (26.4)
Bleeding-related death within 72 hours*	14 (5.3)	19 (7.2)
In-hospital mortality	61 (23.3)	57 (21.5)

* Not associated with the occurrence of an identified thrombotic event.

Subgroup analyses revealed a numerical difference in mortality rate between patients who received high and low dose andexanet. This imbalance was likely due to a higher proportion of patients with a history of cardiac failure (28% vs 14%) and a greater mean

hematoma volume in the high dose andexanet group compared with the low dose andexanet group. Heart failure is associated with increased mortality rates (Javalkar et al 2020) and hematoma volume is a strong predictor for both short- and long-term mortality in patients with intracerebral hemorrhage (LoPresti et al 2014).

1.4.4.3 Adverse Events of Special Interest

In the setting of an emergent, life-threatening hemorrhage, where patients have an increased thrombotic risk above their baseline after reversal, thrombotic events are an adverse drug reaction of andexanet, and the risk of thrombotic events is included in the boxed warning of the USPI. Thrombotic events were evaluated as an adverse event of special interest in ANNEXA-I.

In ANNEXA-I, the proportion of patients with a thrombotic event confirmed by adjudication through 30 days post-randomization was higher in the andexanet group than in the usual care group (Table 4). However, the event rate in the andexanet group was similar to the frequency observed in patients with adjudicated acute major bleeding events in ANNEXA-4 (10.5%), and in line with the rate stated in the USPI.

There was a numerical difference in thrombotic events leading to death. Confounding events were identified in the andexanet arm and in the 2 cases within the usual care group, one received no therapy to reverse the effects of their anticoagulation (see Section 7.7). Additionally, all of these events that led to death in andexanet group occurred on Day 16 or later, except one occurring on Day 2 confounded by multi-trauma and multiple comorbidities.

In patients who experienced at least one thrombotic event, the median time to onset of their first event was 3 days in the andexanet group and 14 days in the usual care group (see Table 29). During the first 3 days, 14 out of 27 patients in the andexanet group had their first event, compared to 1 out of 15 patients in the usual care group. This notable difference is due to the potent reversal effect of andexanet necessary for hemostasis.

Table 4: ANNEXA-I Overview of Adjudicated Thrombotic Events (Safety Set)

Adjudicated Event, n (%)	Andexanet (N=262)	Usual Care (N=265)
Any adjudicated thrombotic event	27 (10.3)	15 (5.7)
Ischemic stroke	17 (6.5)	4 (1.5)
Myocardial infraction	11 (4.2)	4 (1.5)
Arterial systemic embolism	3 (1.1)	2 (0.8)
Pulmonary embolism	1 (0.4)	6 (2.3)
Deep vein thrombosis	1 (0.4)	2 (0.8)
Thrombotic event leading to death	6 (2.3)	2 (0.8)

Importantly, among the patients who received at least one dose of any anticoagulant as a prophylactic measure, similar rates of thrombotic events were observed in the andexanet and usual care groups (see Figure 27). These results show that re-anticoagulation can prevent thrombotic events and confirm the importance of restarting anticoagulation as soon as medically appropriate, in line with the approved prescribing information (USPI). Re-anticoagulation is further discussed in Section 7.7.3.

No new important immunogenicity findings were identified in ANNEXA-I (see Section 7.8) and consistent with results from ANNEXA-4, no neutralizing antibodies against FX or FXa were identified.

1.5 Benefit Risk Conclusions

Andexanet is a vital component of the bundle of care used by emergency physicians to rapidly reverse FXa inhibitors and manage uncontrolled, life-threatening bleeding events. While early thrombotic events are a known risk, they are manageable within the comprehensive acute care setting, where critical care teams are fully equipped to address these complications, and re-initiation of anticoagulation therapy is recommended once the patient is stabilized to prevent future events.

The efficacy results from ANNEXA-I provide clinical evidence of superior hemostatic efficacy with andexanet compared to usual care, supporting an application for full approval. Treatment with andexanet resulted in a statistically significant and clinically relevant improvement in effective hemostasis at 12 hours compared to usual care. This benefit was consistently observed across sensitivity analyses and the exploratory patient subgroup analyses for the primary endpoint. In addition, andexanet confirmed the findings from ANNEXA-4 demonstrating significant and rapid reductions in anti-FXa activity compared with usual care.

The safety profile in ANNEXA-I is in-line with the established profile from the andexanet clinical development program and consistent with the mechanism of action and information in the USPI. No new safety signals or adverse drug reactions were identified.

Safety data from ANNEXA-I support an acceptable safety profile of andexanet in the setting of uncontrolled and life-threatening bleeding events that is consistent with the current label. Patients receiving FXa inhibitors are at an increased risk of thrombotic events following reversal of anticoagulation due to underlying baseline risk factors as well as the life-threatening bleeding prothrombotic state and subsequent risks incurred from hospitalization and/or clinical concurrent conditions typical in hospitalized patients. In the emergent life-threatening bleeding situation, achievement of hemostasis and stabilization of the patient is paramount—high potency and rapid reversal of anticoagulant is a requirement. However, consistent with its mechanism of action, andexanet was associated with a higher rate of thrombotic events compared to usual care. Data from ANNEXA-I confirm the importance of restarting anticoagulation as soon

as medically appropriate. The 30-day mortality rates were similar between groups, and reasons for death in ANNEXA-I are in line with what has been observed in other studies. Overall, andexanet provides superior hemostatic efficacy compared to usual care in patients with a life-threatening or uncontrolled bleeding event after receiving a direct oral FXa inhibitor, with an acceptable and consistent safety profile.

ANNEXA-I provides evidence supporting a positive benefit-risk profile and the conversion to full approval of the currently approved indication and posology for andexanet. ANNEXA-I confirmed the findings and positive benefit-risk previously acknowledged in ANNEXA-4 and demonstrate the clinical benefit of andexanet in patients who experience life-threatening or uncontrolled bleeding in emergency situations.

2 BACKGROUND AND UNMET NEED

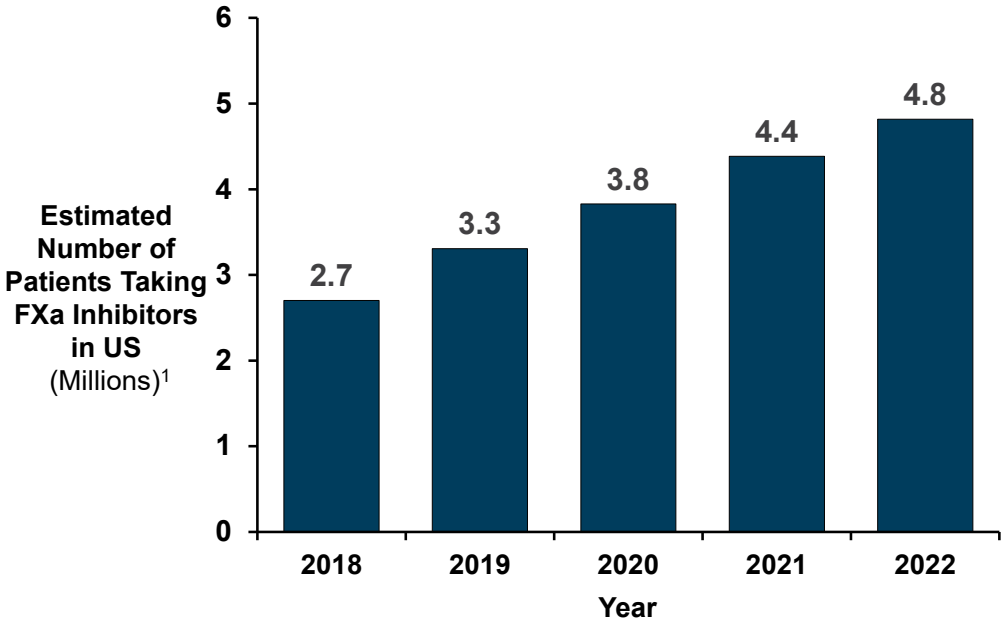
Summary

- Oral FXa inhibitor anticoagulants are increasingly used to manage medical conditions that have an underlying thrombotic risk.
- Annually, approximately 3% to 5% of patients on FXa inhibitors experience life-threatening or uncontrolled bleeding requiring hospitalization annually; GI, ICrH, and trauma-related bleeds most commonly lead to hospitalizations.
- For patients presenting with FXa inhibitor major bleeding, life-threatening bleeding, emergency physicians use a multi-faceted approach that integrates fast-acting, effective therapies including blood pressure control, surgical intervention as needed, and anticoagulant reversal to manage the immediate risk of death.
- Reversing FXa inhibition re-exposes patients to their underlying thrombotic risk, which is further heightened by the bleeding event itself.
- In the setting of ICrH, hematoma expansion is a well-established predictor of poor clinical outcomes including neurological deterioration, poor functional outcomes and increased risk of mortality.
- 4F-PCC is used off-label in the setting of direct oral FXa inhibitor related bleeds however is only approved and indicated for warfarin reversal.
- Andexanet is the only approved FXa specific reversal agent for patients taking apixaban and rivaroxaban who experience life-threatening bleeds.

2.1 Major Bleeding Events in Patients Receiving Anticoagulation Therapy

Oral FXa inhibitor anticoagulants are increasingly being used to manage medical conditions with an underlying thrombotic risk, such as atrial fibrillation and venous thromboembolism (Botticelli Investigators et al 2008; Burness and Perry 2014; January et al 2019; Lip et al 2017). In 2022, an estimated 4.8 million patients in the US were taking oral FXa inhibitors, and this number is expected to continue to rise (Figure 7).

Figure 7: Estimated Number of Patients in the US Taking Oral FXa Inhibitors over Time (2018 – 2022)

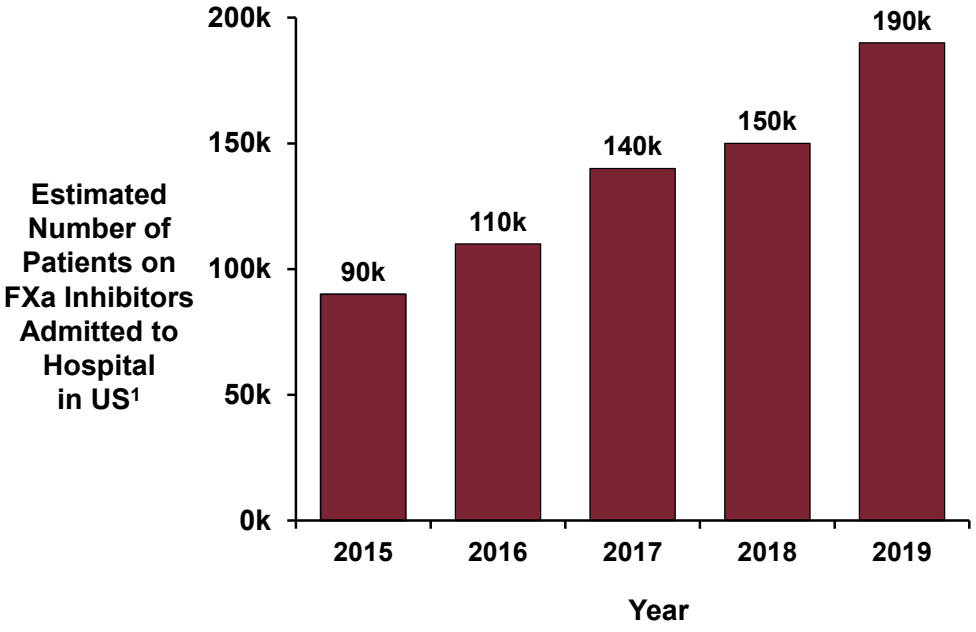


FXa: activated factor X. US: United States.
1.(Centers for Medicare and Medicaid Services 2022)

While oral FXa inhibitors are effective in managing the underlying condition, a major limitation of anticoagulant use has been the lack of reversal agents for use in cases of severe or life-threatening bleeding events. The incidence of acute major bleeding events related to direct oral FXa inhibitors ranges from 3 to 5 per 100 patient-years (Crawley and Anderson 2020). These major bleeding events can occur across various body sites and all have been shown to manifest as acute major bleeds leading to hospitalization.

As the use of FXa inhibitors increases, so does the number of hospital admissions for bleeding events linked to these medications. As illustrated in Figure 8, there has been a greater than 2-fold increase in FXa inhibitor-related hospitalization due to life-threatening bleeding from 2015 to 2019. These hospitalizations are primarily due to gastrointestinal, ICrH, and trauma-related bleeds.

Figure 8: Estimated Number of Patients on FXa Inhibitors Admitted to Hospital in the United States (2015 – 2019)



FXa: activated factor X.
2019 data From 1 October 2018 to 30 September 2019.
Source: (Truven Health Analytics 2019)

2.2 Intracranial Hemorrhage

While major bleeding events can occur at various sites, ICrH events are of particular interest in a clinical trial setting because of the established methods for objective measurement of hematoma size and expansion allowing the events and treatments to be evaluated.

2.2.1 Pathology and Epidemiology

Many ICrH events may be caused by cerebral small vessel disease, also termed hypertensive arteriopathy or arteriosclerosis (McGurgan et al 2020), and the phenomenon of thromboses in conjunction with ICrH may imply that the presence of an ICrH itself can be viewed as a risk marker for arterial ischemic events (Murthy et al 2021).

Risk factors for ischemic stroke and ICrH such as age and hypertension, age, pre-morbid functional state, initial GCS, blood pressure, lead to an elderly patient population with comorbidities with risk for both hematoma expansion and thrombotic events.

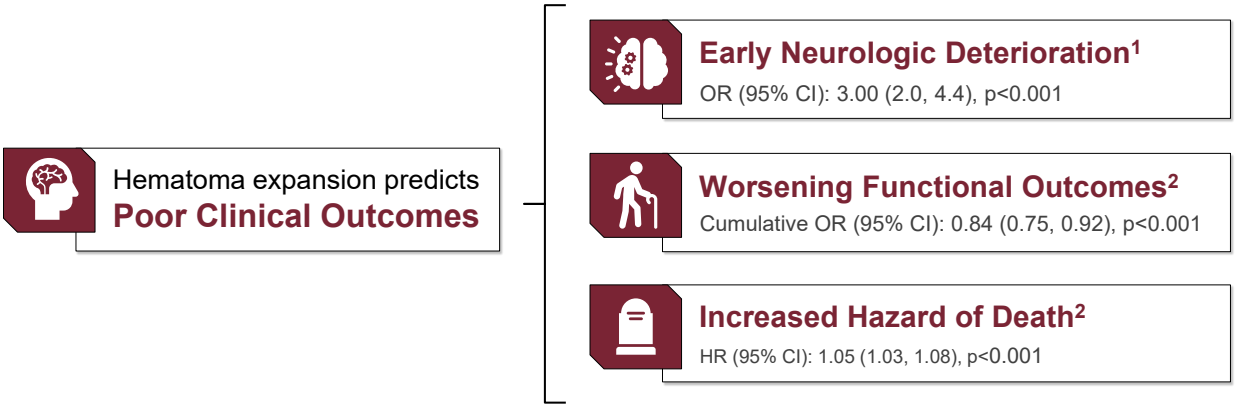
2.2.2 Prognosis

Patient prognosis after an ICrH depends on many factors. In cases of acute intracerebral haemorrhage, time is a critical determinant of patient outcomes (Al-Shahi Salman et al 2018). Studies have demonstrated a clear inverse relationship between time to treatment and the probability of significant hematoma expansion (> 6 mL), with the majority of expansion occurring within the first 3 hours of the bleed. This underscores the urgent need for rapid, targeted therapies that restore physiologic coagulation and help prevent further hematoma growth. Larger hematoma volume at baseline is associated with increased risk of hematoma expansion and mortality (Broderick et al 1993).

Within the ICrH population, patients at greatest risk for hematoma expansion are most likely to have poor clinical outcomes (Davis et al 2006; Held et al 2015). Hematoma expansion is associated with early neurological deterioration, worsening of functional outcomes, and increased risk of death (Figure 9). As reported by Delcourt et al (2012), the volume of intracerebral hemorrhage is strongly associated with mortality risk at 90 days. Results from the INTERACT 1 study, which investigated the impact of rapid intensive blood pressure lowering on hematoma expansion in patients presenting with a CT-confirmed spontaneous intracerebral hemorrhage, demonstrated that patients with larger increases in hematoma volumes, whether evaluating absolute increases or proportional increases, were at a significantly higher risk of death or dependency (Delcourt et al 2012). For every 1 mL increase in hematoma volume, there is a 5% higher risk of death or dependency. The importance of hematoma volume poor prognosis is supported by multiple studies. The multivariable-adjusted regression analyses reported by Dowlatshahi et al (2011) confirmed that across a range of hematoma expansion definitions, hematoma expansion independently predicted poor outcome (odds ratio [OR] of 2.73 [95% confidence interval (CI): 1.70, 4.39] for hematoma expansion ≥ 33% (similar to the ≥ 35% criteria in the ANNEXA-I primary endpoint); OR of 3.98 [95% CI: 1.94, 8.18] for hematoma expansion ≥ 12 mL). Together, these data indicate that the size of the hemorrhage is an important prognostic factor for survival.

The location of the bleed is also known to impact patient outcomes, with infratentorial bleeds (particularly brainstem bleeds) having a worse prognosis (Davis et al 2006).

Figure 9: Poor Outcomes Associated with Hematoma Expansion

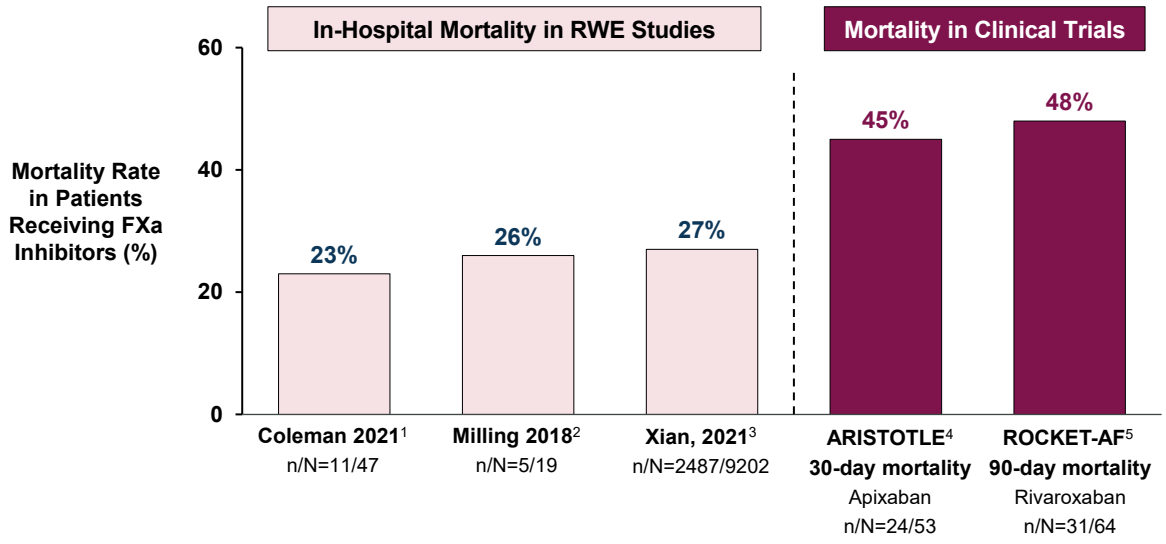


CI: confidence interval; HR: hazard ratio; OR: odds ratio.
1. (Kuohn et al 2022); 2. (Davis et al 2006)

Multiple studies have characterized the risk of mortality associated with an intracerebral hemorrhage in patients receiving FXa inhibitors. The results from 3 large retrospective and registry-based studies involving patients hospitalized for FXa inhibitor–related or nontraumatic intracerebral hemorrhage show in-hospital mortality rates ranging from 23% to 27% (Figure 10). Additionally, clinical trial data from studies of apixaban and rivaroxaban highlight the severity of ICrH events in patients receiving FXa inhibitors.

In the apixaban clinical trial, 30-day mortality rates were 45%, and in the rivaroxaban clinical study, all-cause mortality through 90 days approached 50%.

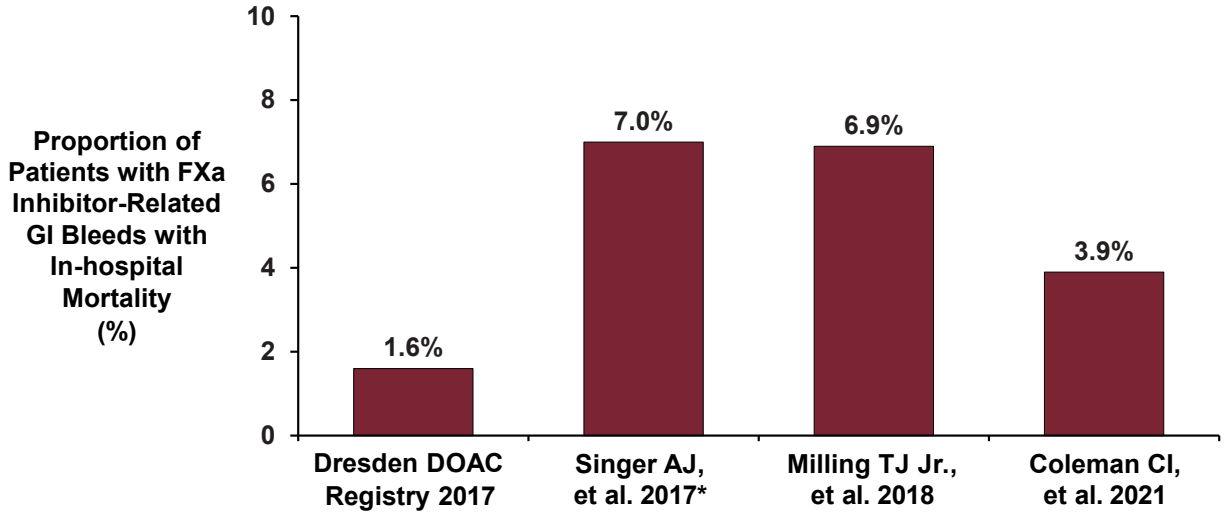
Figure 10: Mortality Rates in Patients Receiving FXa Inhibitors – RWE Studies and Clinical Trials



FXa: activating factor X; RWE: Real-World Evidence.
1. (Coleman et al 2021); 2. (Milling et al 2018); 3. (Xian et al 2021) 4. (Held et al 2015); 5. (Hankey et al 2014)

FXa inhibitors are also linked to significant mortality in major GI bleeds. While in general, fewer deaths occur from GI-related major bleeds compared to other bleeding events, FXa-related GI bleeds are concerning because they are more prominent compared to other bleed types, and they can be fatal. In-hospital mortality associated with FXa-related GI bleeds range from 1.6% to 7% (Figure 11). In addition, studies of patients who experience upper GI bleeds have reported even higher in-hospital mortality rates, ranging from 12% to 25%(Menichelli et al 2024). Because of this, in cases where quick intervention is needed, FXa specific reversal agents are important for restoring hemodynamic coagulation and reducing the risk of mortality.

Figure 11: In-Hospital Mortality Rates in Patients with FXa Inhibitor-Related Gastrointestinal Bleeds



FXa: activated factor X; GI: gastrointestinal.
* Rate of in-hospital mortality higher among patients with upper GI bleeds, ranging from 12–25%.1
1.(Menichelli et al 2024)

Rapid intervention to control the bleeding is critical. In ICrH, a shorter time interval between the onset of symptoms and clinical presentation is associated with an increased risk of hematoma expansion, with the greatest risk within the first 3 hours after symptom onset (Brott et al 1997). The expected progression rate of an intracerebral hemorrhage at therapeutic FXa inhibition is not fully known but one study reported a 38% incidence of hematoma expansion at a median follow-up time of 21 hours after presentation (Purrucker et al 2016), suggesting that bleeding should be counteracted early in the process. The need for early intervention was also recently demonstrated by Sheth et al (2024) with results showing that earlier anticoagulation reversal was associated with improved survival for patients with intracerebral hemorrhage.

In ICrH, the reported 30-day mortality rates for patients are 30% to 55% (Apostolaki-Hansson et al 2021; Balami and Buchan 2012; Giugliano et al 2014; Hankey et al 2012; Held et al 2015), and half of these deaths occur in the acute phase, particularly within the first 48 hours. Given the most active rebleeding takes place early on and can lead to death and disability, early and acute reversal interventions play a critical role in stabilizing the patient.

2.2.3 Complications

Thrombotic events, including both arterial and venous subtypes, are a recognized complication after an ICrH. The increased risk of thrombotic events emerges early in the acute phase of ICrH and persists well into the future for survivors, with a peak in the first and second months following the bleeding event (Murthy et al 2020). The pathophysiology of major hemorrhage, especially associated with trauma, may predispose the patient to a prothrombotic state of coagulation that would be considered additive with their underlying thrombotic risk factors (Moore et al 2021). Further, as recognized in the literature, there may be several other confounders that are contributory towards the formation of thrombotic events in these acutely, critically unwell patients, such as but not limited to neurological function, intubation, immobility, prolonged length of hospital stay and clinical concurrent events such as infection(Li and Murthy 2022), as well as the absence of any re-anticoagulant after bleeding (Zhou et al 2018).

2.3 Current Treatment Options for Anticoagulated Patients Presenting with Major Bleeding

In the management of anticoagulated patients with ICrH, a primary therapeutic goal is the prevention of hematoma expansion, which has been strongly associated with morbidity and mortality (Davis et al 2006; Dowlatshahi et al 2011; Sarode et al 2013). The current understanding is that intracerebral bleeding in patients taking oral anticoagulation (OAC) reflects spontaneous bleeding that is exacerbated by anticoagulation. Therefore, OAC sustains intracerebral hematoma formation but does not cause it. Reversal therapy is therefore tailored to address the exacerbated bleeding risk in OAC associated ICrH (Steiner et al 2017).

Andexanet is the only approved FXa specific reversal agent for patients taking apixaban and rivaroxaban who experience life-threatening bleeds (Table 5). Four-factor PCC is approved and indicated for warfarin reversal but is not approved as a reversal of direct oral FXa inhibitors. Additionally, similar to andexanet, 4F-PCC has a known risk of thrombosis as indicated in the USPI. Several non-specific potential reversal agents have been studied in patients who have bleeding events on direct oral FXa inhibitors, eg, fresh frozen plasma, 3-factor PCC, 4F-PCC, activated PCC, and recombinant activated factor VII (Suryanarayan and Schulman 2014).

Table 5: Interventions to Reverse Anticoagulation Therapy

Anticoagulant	Class	Intervention	Mechanism of Action	Time to Onset
Apixaban[1]	FXa inhibitor	Andexxa	Reverses FXa inhibition	2 minutes
Rivaroxaban[1]				
Warfarin[2–6]	VKA	4F-PCC[2,4-6]	Replaces factors II, VII, IX and X	8 hours
Dabigatran[7]	Direct thrombin inhibitor	Idarucizumab7	Restores thrombin inhibition	5 min

1. (AstraZeneca 2024); 2. (Ansell et al 2008); 3.(FAMHP 2020); 4. (Octapharma 2023); 5. (Ghadimi et al 2016); 6. (CSL Behring GmbH 2013). 7.(Boehringer Ingelheim International GmbH 2015)

2.4 Guidelines for Hemostasis in Major Bleeding Events

When patients present with an acute major bleed, time is of the essence. For this reason, treatment guidelines of ICrH emphasize the need to introduce multiple interventions. This has been further developed in recent expert consensus papers as part of a rapid bundle of care in an effort to minimize hematoma expansion and maximize patient survival (Parry-Jones et al 2024; Yakhkind et al 2024). Physicians and critical care teams deploy this bundle of care consisting of fast-acting interventions, such as blood pressure management, targeted anticoagulant reversal agents, and surgical procedures as applicable. Each element is designed to act swiftly to stabilize the patient and control the bleed. Key components include:

- **Door** (at presentation): Stabilize patient, rapid imaging, coagulation tests
- **< 30 min:** Reverse anticoagulant, start intensive blood pressure lowering
- **< 60 min:** systolic blood pressure < 140, consult neurosurgery, achieve temp < 37.5°C
- **7 days:** Maintain systolic blood pressure < 140, temp < 37.5°C, maintain normoglycemia
    - Minimize post-reversal thrombotic risks
        - Early venous thromboembolism prophylaxis per American Heart Association guidelines
        - Restart anticoagulant therapy as early as possible based on individualized risk benefit assessment

American and European stroke guidelines recommend the use of oral anticoagulant reversal treatment to potentially reduce hematoma expansion when a patient presents with an acute majoring bleeding event (Christensen et al 2019; Greenberg et al 2022). Since approval of andexanet under the accelerated approval pathway, multiple national

and international guidelines have supported the use of andexanet for life-threatening bleeding related to FXa inhibitors (Baugh et al 2020; Greenberg et al 2022; Tomaselli et al 2020).

2.5 Patient Unmet Medical Need

Patients on direct oral FXa inhibitors who experience acute major bleeding events need effective reversal agents to rapidly restore proper coagulation and stop the bleeding. Timely intervention is crucial to prevent complications such as hematoma expansion and other forms of hemorrhage. The increasing number of hospital admissions due to bleeding events underscores the urgent need for specific reversal agents in these emergency situations. Andexanet rapidly and effectively neutralizes the effects of FXa inhibitors, offering a targeted solution as part of a bundle of care for managing bleeding events. For this reason, andexanet has become a recognized and essential treatment option for clinicians, enabling fast and effective management of bleeding events as part of the bundle of care deployed in emergency settings.

3 PRODUCT DESCRIPTION

Summary

- Andexanet is an injectable, inactivated, recombinant analog of endogenous human FXa, developed to rapidly reverse FXa inhibition and restore physiologic coagulation.
- Andexanet is indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding and has been available in the US since 2018.
- Andexanet exerts its procoagulant effect by binding and sequestering the FXa inhibitors, rivaroxaban and apixaban, thereby neutralizing their anticoagulation effects and restoring thrombin generation.

3.1 Product Overview

Andexanet is an injectable, inactivated, recombinant analog of endogenous human FXa, developed to rapidly and potently reverse FXa inhibition and restore physiologic coagulation. Clinical studies to date have shown that andexanet rapidly reverses FXa inhibition in healthy volunteers and in bleeding patients, including those with ICrH.

Andexanet has been available in the US since receiving accelerated approval in 2018. As of 31 July 2024, approximately 64,370 patients have been treated with andexanet worldwide, including 34,551 patients in the US.

3.2 Proposed Indication and Posology

Andexanet alfa is indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. With the conversion to full approval, the current language in the labeling describing accelerated approval would be removed.

There are 2 dosing regimens:

- Low dose: 400 mg IV bolus, followed by a continuous infusion of 480 mg at 4 mg/min for approximately 120 minutes
- High dose: 800 mg IV bolus, followed by a continuous infusion of 960 mg at 8 mg/min for approximately 120 minutes

The recommended dosing of andexanet is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor, as described in Table 6. To completely reverse anti-FXa activity, the andexanet concentration must be in molar excess over the FXa inhibitor concentration.

Table 6: Andexanet Dose Based on Rivaroxaban or Apixaban Dose

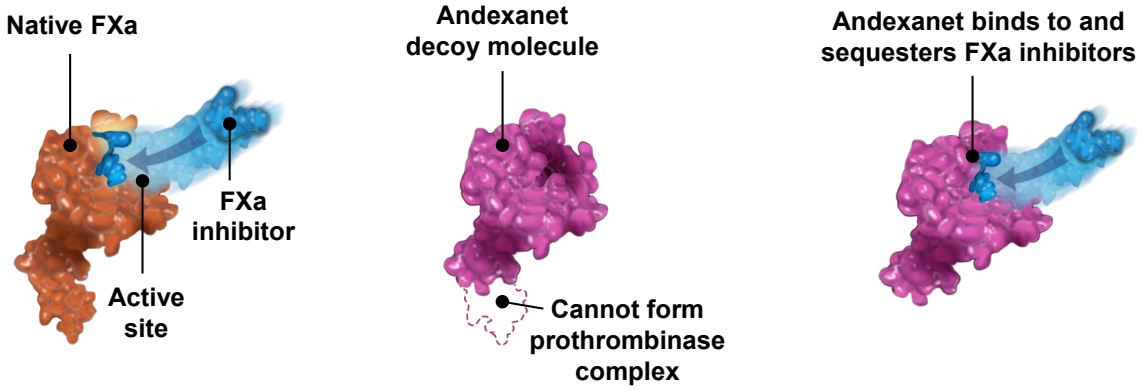
FXa Inhibitor	FXa Inhibitor Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg or Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg or Unknown	High Dose	

FXa: activated factor X.

3.3 Mechanism of Action

As a modified version of FXa, andexanet binds directly FXa inhibitors with high affinity, but lacks the coagulation activity of native FXa (Figure 12). Andexanet rapidly restores coagulation when measured as anti-FXa activity and thrombin generation and reduces unbound FXa inhibitor concentrations in patients treated with the direct oral FXa inhibitors apixaban, rivaroxaban, and edoxaban. Results from the ANNEXA-A and ANNEXA-R studies demonstrated that reversal occurs within 2 minutes of administration (see Figure 2).

Figure 12: Andexanet Mechanism of Action



- FXa inhibitors target active site of FXa, blocking enzymatic activity and preventing thrombin generation
- Andexanet acts as a decoy and binds directly to FXa inhibitors
- Rapidly reduces free-plasma concentration
- Neutralizes anticoagulant effect

FXa: activated factor X.

A summary of the pharmacokinetic (PK) properties of andexanet in healthy volunteers is shown in Table 7.

Table 7: Summary of Pharmacokinetic Parameters with High and Low Dose Andexanet

Geometric Mean (% Coefficient of Variation) [Range]	Low Dose (N=11)	High Dose (N=10)
$AUC_{0-\infty}$ (hr*µg/mL)	200.5 (16.3) [153.4 - 255.6]	572.9 (16.0) [467.1 - 783.9]
C_{max} (µg/mL)	76.6 (17.5) [61.1 - 100.1]	206.6 (18.8) [158.9 - 280.5]
Clearance (L/hr)	4.4 (16.3) [3.4 - 5.7]	3.1 (16.0) [2.3 - 3.8]
$T_{1/2}$ (hr)	3.3 (15.0) [2.3 - 4.0]	2.7 (20.0) [1.9 - 3.4]
V_{ss} (L)	4.4 (17.6) [3.3 - 5.7]	3.0 (23.3) [2.2 - 5.0]

$AUC_{0-\infty}$: area under the concentration time-curve from time zero to infinity; C_{max}: maximum observed concentration; hr: hour; L: liter; $t_{1/2}$: terminal phase half-life; V_{ss}: volume of distribution at steady state.

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- Andexanet was granted accelerated approval by the FDA in May 2018 based on data demonstrating that andexanet rapidly reverses FXa inhibition in healthy volunteers and non-comparative data from patients who had acute major bleeding while receiving an FXa inhibitor.
- ANNEXA-I was conducted to fulfil post-marketing requirements to convert from accelerated to traditional, full approval of andexanet.
- ANNEXA-I is the first randomized controlled study of andexanet in patients with life-threatening or uncontrolled bleeding after receiving a direct oral FXa inhibitor.

4.1 Regulatory Milestones

Andexanet was granted breakthrough designation on 22 November 2013 and orphan drug designation on 23 February 2015. Accelerated Approval was granted by the FDA on 03 May 2018 and initial conditional marketing authorization by the European Commission (including Great Britain) on 26 April 2019 for neutralizing the anticoagulant effects of apixaban and rivaroxaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. Additional interactions with FDA are summarized in Table 8.

Table 8: Key Interactions between AstraZeneca and FDA on ANNEXA-I

Date	Description
May 2018	Initial BLA Review ANNEXA-I trial design and endpoints agreed with FDA during BLA review
July 2022	Type C Meeting Statistical alignment of interim approach with 450 patients and data integrity plans
Dec 2023	Pre-sBLA interaction Content and format of planned sBLA agreed and aligned
January 2024	sBLA submitted
March 2024	Application Orientation Meeting

BLA: Biologics License Application; FDA: Food and Drug Administration; sBLA: supplemental Biologics License Application.

Andexanet is approved in 45 countries, 7 of which are full approvals, where ANNEXA-I is not a PMR. Full approvals are in Japan, Brazil, Mexico, Switzerland, India, Kuwait, and Saudia Arabia, as well as in Hong Kong. Andexanet is marketed in 24 countries.

4.2 Clinical Development Program

To date, andexanet has been studied in 553 adult healthy volunteers in Phase I to Phase 3 studies, as well as in 741 adult patients who experienced an acute major bleeding event while receiving an FXa inhibitor in the completed Phase 3b/4 ANNEXA-4 and Phase 4 ANNEXA-I studies. Andexanet has also been studied in 10 patients requiring urgent surgery in ANNEXA-S.

Approvals of andexanet to date were based on data demonstrating that andexanet rapidly reverses FXa inhibition from Phase 1 to 3 studies in healthy volunteers and non-comparative data from patients who had acute major bleeding while receiving an FXa inhibitor in ANNEXA-4. As a condition of Accelerated Approval in the US, a PMR was issued to verify the hemostatic effect of andexanet as described in the May 2018 Approval letter (https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm):

> *Study 18-513: "A Phase 4 randomized trial of ANDEXXA in acute intracranial hemorrhage in patients receiving oral factor Xa inhibitors"*
>
> *This open-label, randomized trial will include at least 440 adult patients who developed acute intracranial hemorrhage following the treatment with rivaroxaban, apixaban, or edoxaban 15 hours or less prior to randomization. The enrolled patients will be administered ANDEXXA (high or low dose) or standard of care other than ANDEXXA according to 1:1 randomization scheme. To describe and verify the hemostatic effect of ANDEXXA, patients will be assessed with the National Institute of Health Stroke Scale and computed tomography or magnetic resonance imaging at 12-hours post-randomization. The trial assessments will also include evaluation of occurrence of the safety events of special interest, including but not limited to: stroke, transient ischemic event, acute myocardial infarction, deep vein thrombosis, pulmonary embolism, arterial systemic embolism, sudden death, and events suspicious for thrombosis, embolism, and ischemia—all to be observed at least 3 days for immediate occurrence and at least 30 days with weekly intervals for delayed occurrence. The assessments of the hemostatic effect will be made by an adjudication committee blinded to the treatment allocation.*

ANNEXA-I was the first randomized, controlled clinical study to compare andexanet with usual care regarding efficacy and safety in patients with acute ICrH, a condition of life-threatening and uncontrolled bleeding that has an established method for objective measurement of hematoma size and expansion. ANNEXA-I also aimed to fulfil post-marketing requirements from specific regulatory authorities.

ANNEXA-I was conducted in patients with acute ICrH as this represents a condition of life-threatening and uncontrolled bleeding with an established method for objective measurement of hematoma size and expansion. Studying hematoma expansion in acute ICrH in patients receiving a direct oral FXa inhibitor enables objective assessment

of acute bleeding cessation. Assessing bleeding cessation in patients with bleedings in other locations is more difficult and subjective (Connolly et al 2019; Milling et al 2023).

5 STUDIES SUPPORTING ACCELERATED APPROVAL OF ANDEXANET

Summary

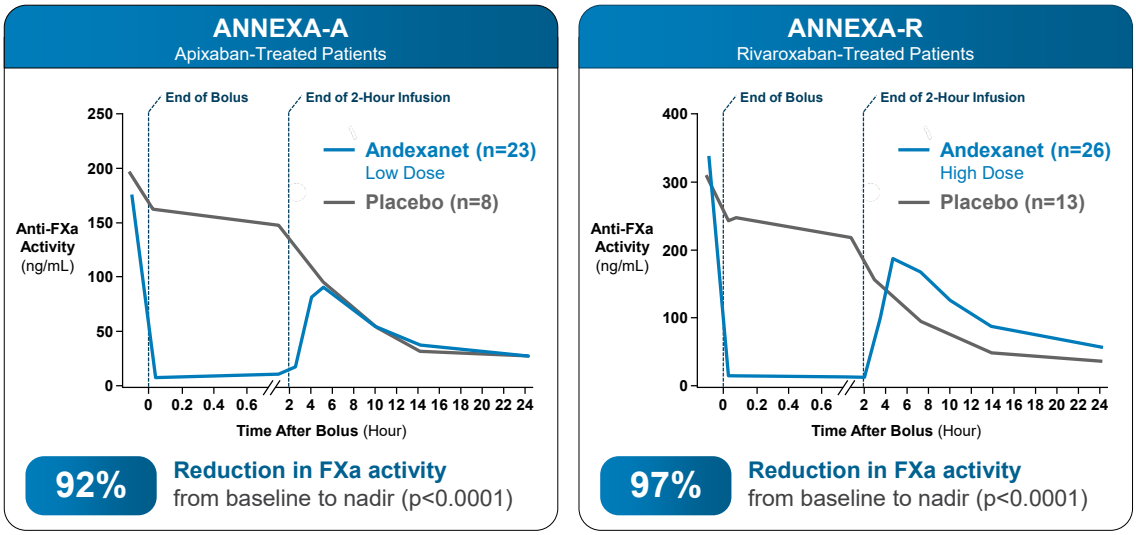
- In ANNEXA-A and ANNEXA-R, andexanet rapidly and significantly reversed the anti-FXa activity of apixaban and rivaroxaban, reduced unbound apixaban and rivaroxaban concentrations, and restored normal thrombin generation.
- In ANNEXA-4, andexanet treatment rapidly reduced anti-FXa activity with acute major bleeding while taking FXa inhibitors.
    - The median reduction from baseline was 93.3% in patients on apixaban and 94.1% in patients on rivaroxaban.
    - Excellent or good hemostasis was achieved in 80.0% of patients in the efficacy population.
- In ANNEXA-4, andexanet had an acceptable safety profile in patients with acute major bleeding, and the rate of AEs were within the expected range given the severely ill and highly vulnerable study population.
    - 10.5% of patients experienced an adjudicated thrombotic event; the rate of thrombotic events was lower in patients who resumed anticoagulation therapy (4.9%) than those without anticoagulation prophylaxis (20.7%).
- A growing body of peer-reviewed RWE supports the use of andexanet.

5.1 ANNEXA-A and ANNEXA-R

The Phase 3 studies ANNEXA-A and ANNEXA-R were randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of andexanet in older healthy volunteers dosed to steady state plasma levels with apixaban or rivaroxaban, respectively. Both studies were conducted from 2014 and 2015. In ANNEXA-A and ANNEXA-R, the anticoagulant was dosed to steady state over 4 days (rivaroxaban 20 mg once daily) or 3.5 days (apixaban 5 mg twice daily) before administration of andexanet or placebo on Day 4. In both studies, andexanet was administered either as an IV bolus (Part 1) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). The andexanet doses in both studies (400 mg bolus ± 4 mg/min infusion for 2 hours in ANNEXA-A; 800 mg bolus ± 8 mg/min infusion for 2 hours in ANNEXA-R) were intended to ensure a robust reduction in anti-FXa activity.

In both studies, marked changes in anti-FXa activity, thrombin generation, and unbound fraction of FXa inhibitors were observed. A single IV bolus of andexanet rapidly and significantly reversed the anti-FXa activity of apixaban and rivaroxaban, reduced unbound apixaban and rivaroxaban concentrations, and restored normal thrombin generation (Figure 13). These effects were sustained during the follow-on infusion.

Figure 13: Andexanet Anti-FXa Activity in ANNEXA-A and ANNEXA-R



Low Dose = 400-mg bolus + 480 mg × 2-hr infusion; High Dose = 800-mg bolus + 960 mg × 2-hr infusion; Placebo = bolus + 2-hr infusion

FXa: activated factor X; hr: hour

In ANNEXA-A, a 400 mg bolus was sufficient to result in a mean 93.9% reduction in anti-FXa activity and restore thrombin generation in all 24 healthy volunteers dosed with andexanet. Similarly, a 400 mg bolus plus 4 mg/min infusion resulted in a 92.3% reduction in anti-FXa activity and restored thrombin generation in all 23 healthy volunteers dosed with andexanet.

Analogous findings were observed in ANNEXA-R. Of 53 healthy volunteers dosed with either an 800 mg bolus administered alone (92.2% anti-FXa reduction) or with an 8 mg/min infusion (96.7% reduction), all but one had restoration of thrombin generation.

In both ANNEXA-A and ANNEXA-R, there were no thrombotic events, SAEs, or severe AEs reported. Andexanet doses were well tolerated and there were no significant safety findings.

Taken together, these data indicate that andexanet, delivered at a dose known to produce a molar excess relative to the anticoagulant, resulted in greater than 90% reductions in anti-FXa activity and restoration of thrombin generation in 99 of 100 healthy volunteers treated. The efficacy results of ANNEXA-A and ANNEXA-R unequivocally demonstrated the effect of andexanet on the surrogate endpoint of anti-FXa activity and were key findings in support of the conditional approval of andexanet.

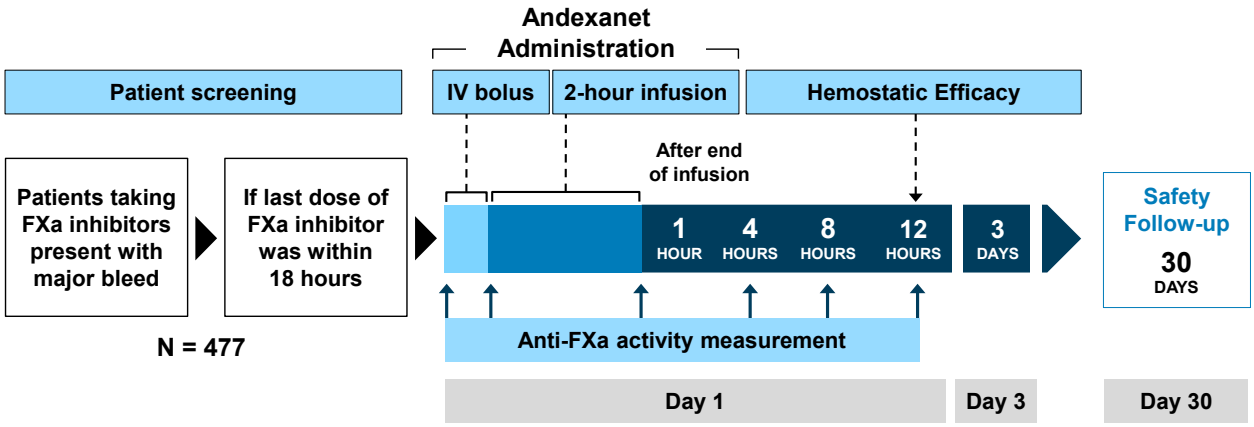
5.2 ANNEXA-4

5.2.1 Study Design

The Phase 3b ANNEXA-4 study was a single-arm, open-label study evaluating the efficacy and safety of andexanet in patients with acute major bleeding while taking FXa inhibitors. Eligible patients for the study (those aged ≥ 18 years, with acute major bleeding within 18 hours after the last dose of apixaban, rivaroxaban, edoxaban, or enoxaparin) were treated with either a low or a high dose of andexanet, depending on the identity, amount, and timing of the last dose of the anticoagulant.

After screening, patients underwent andexanet administration, including a 15-to-30-minute bolus dose, followed by a 2-hour infusion of the drug (Figure 14). Measurements to evaluate hemostatic efficacy were obtained prior to and after the end of bolus administration, at the end of the 2-hour infusion, and at pre-specified timepoints following infusion. Safety, including AEs, adjudicated thrombotic events, immunogenicity, and deaths, was assessed through 30 days.

Figure 14: ANNEXA-4 Study Design



FXa: activated factor X; IV: intravenous.

The co-primary efficacy endpoints were:

- Achievement of effective hemostasis, as judged by the EAC
- Change from baseline in anti-FXa activity to the nadir value during andexanet treatment

Effective hemostasis was determined based on criteria established in a pivotal study of a reversal agent for vitamin K antagonists (Sarode et al 2013).

The secondary objective was to assess the relationship between the 2 co-primary efficacy endpoints.

5.2.2 Study Participants

The efficacy population in ANNEXA-4 included 347 patients, and the safety population included 477 patients.

The mean age of participants was approximately 78 years and approximately 36% of patients were receiving rivaroxaban and approximately half were receiving apixaban (Table 9). The majority of patients presented with an intracranial bleed and 23% presented with a GI bleeding episode.

Table 9: ANNEXA-4 Patient Demographics and Baseline Characteristics

Parameter, n (%)	Safety Population (N=477)	Efficacy Population (N=347)
Age (years); Mean (SD)	77.9 (10.66)	77.8 (10.63)
Female	218 (45.7)	163 (47.0)
White	414 (86.8)	300 (86.5)
Factor Xa inhibitor		
Apixaban	245 (51.4)	172 (49.6)
Rivaroxaban	174 (36.5)	130 (37.5)
Enoxaparin	22 (4.6)	17 (4.9)
Edoxaban	36 (7.5)	28 (8.1)
Site of bleeding		
Intracranial	329 (69.0)	247 (71.2)
Gastrointestinal	109 (22.9)	78 (22.5)

FXa: activated factor X; SD: standard deviation

ANNEXA-4 enrolled a highly comorbid population with 12% of patients having experienced a prior myocardial infarction (MI), 23% with a prior stroke and 17% with a deep vein thrombosis (Table 10).

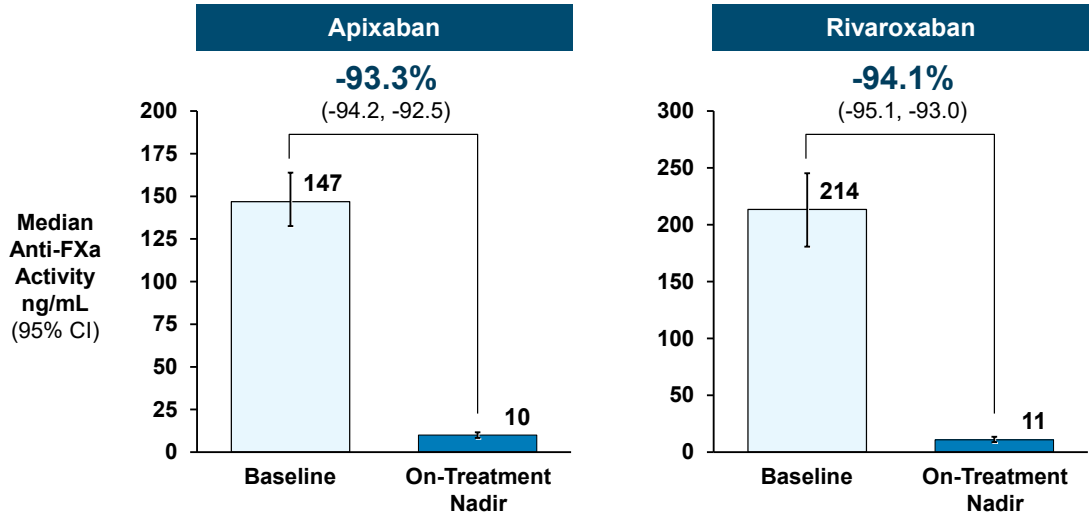
Table 10: ANNEXA-4 Patient Medical History (Safety Population)

Medical History, n (%)	Safety Population (N=477)
Myocardial infarction	59 (12.4)
Stroke	108 (22.6)
Deep vein thrombosis	80 (16.8)
Pulmonary embolism	48 (10.1)
Atrial fibrillation	394 (82.6)
Congestive heart failure	94 (19.7)

5.2.3 Efficacy

Overall, andexanet treatment rapidly reduced anti-FXa activity. Consistent with the healthy volunteer PK/pharmacodynamic (PD) studies, andexanet produced marked reductions in anti-FXa activity in most patients, despite high variance in baseline levels. The median reduction from baseline was 93.3% in patients on apixaban and 94.1% in patients on rivaroxaban (Figure 15). Consistent reductions in anti-FXa activity were observed across subgroups, including baseline FXa inhibitor used and bleeding sites (eg, GI and ICrH).

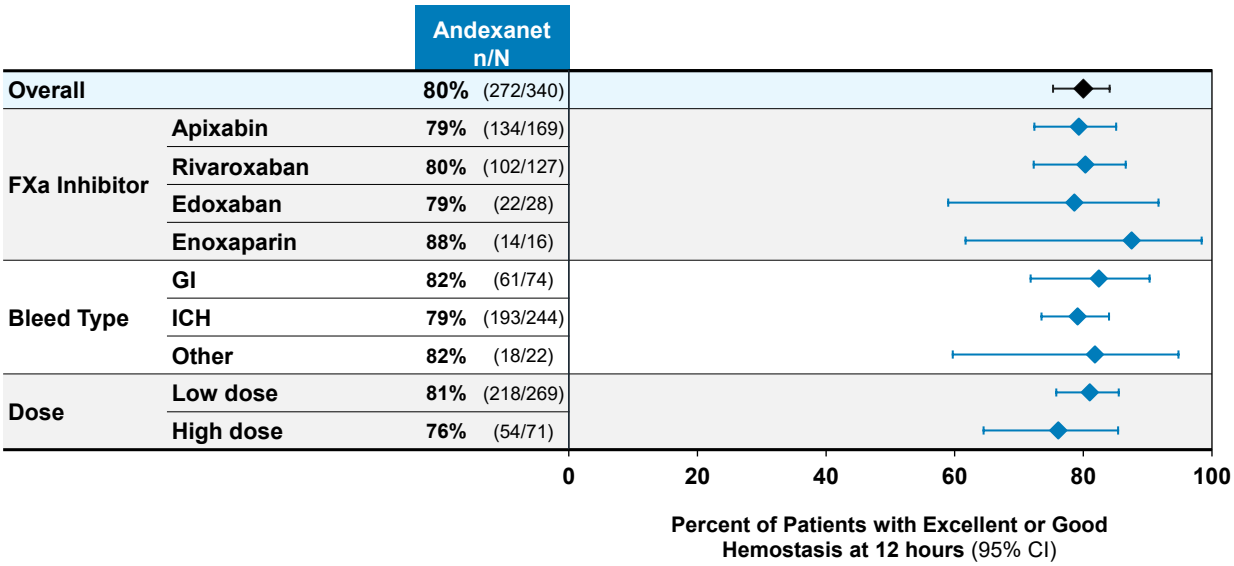
Figure 15: ANNEXA-4 Co-Primary Efficacy Results (Efficacy Population)



CI: confidence interval; FXa: activated factor X.

Excellent or good hemostasis was achieved in 80.0% of patients in the efficacy population. Similar numbers of patients with excellent or good hemostatic efficacy were observed across patients with differing FXa inhibitors and bleed types (Figure 16).

Figure 16: ANNEXA-4 Hemostatic Efficacy (Efficacy Population)



CI: confidence interval; FXa: activated factor X; GI: gastrointestinal; ICH: intracranial hemorrhage.

To analyze the relationship between the co-primary efficacy endpoints, several measures of anti-FXa activity (eg, baseline, nadir, absolute and percent change from baseline) were evaluated in relationship to hemostatic efficacy. The results did not demonstrate a strong relationship between anti-FXa reversal and hemostatic efficacy. Confounding by the low number of patients with non-effective hemostasis and small anti-FXa reductions, variation in bleeding source (venous or arterial), in platelet function, in type of FXa inhibitor, and other patient characteristics may have contributed to the results.

5.2.4 Safety

Andexanet had an acceptable safety profile in patients with acute major bleeding and the rate of AEs were within the expected range given the severely ill and highly vulnerable study population.

Overall, 72.5% of patients experienced at least one AE, and the majority of events were mild-to-moderate in severity (Table 11). Four patients experienced AEs resulting in premature discontinuation of andexanet. Overall, 17% of patients experienced a fatal AE. The 30-day mortality rate for patients with ICrH was 18.2%, which is numerically lower than that reported in contemporary studies in patients with FXa inhibitor-associated ICrH (Williams et al 2023).

Table 11: ANNEXA-4 Adverse Event Overview (Safety Population)

Adverse Event, n (%)	Safety Population (N=477)
Any adverse event	346 (72.5)
AE leading to treatment discontinuation	4 (0.8)
Serious adverse event	200 (41.9)
AE leading to death within 30 days	81 (17.0)
Patients with ICrH	60/329 (18.2)
Patients with GI bleed	15/109 (13.8)
Patients with other bleed	6/39 (15.4)

AE: adverse event; GI: gastrointestinal; ICrH: intracranial hemorrhage.

In ANNEXA-4, 10.5% of patients had a thrombotic event confirmed by adjudication (50/477 patients). Analyses were performed to examine the effect of resuming anticoagulation therapy on thrombotic events. The rate of thrombotic events was lower in patients who resumed anticoagulation therapy than those receiving no anticoagulation prophylaxis (Table 12). These results led to the recommendation in the label to restart anticoagulation as soon as medically appropriate after receipt of andexanet.

Table 12: Adjudicated Thrombotic Events within Day 30 (Safety Population)

Event Population	Safety Population n/N (%)
Adjudicated Thromboembolic event	
Safety Population	50/477 (10.5)
Patients with no anticoagulation as a prophylactic	35/169 (20.7)
After restart of any anticoagulation prior to thrombotic event	15/308 (4.9)
After restarting oral anticoagulation	0/129 (0)

5.2.5 Conclusions

ANNEXA-4 demonstrated a substantial benefit of andexanet as reversal agent in FXa inhibitor-mediated bleeding. When administered to patients with acute major bleeding while taking FXa inhibitors, andexanet was efficacious in restoring physiologic hemostasis and was well tolerated.

6 CLINICAL EFFICACY: CONFIRMATORY STUDY ANNEXA-I

Summary

- The efficacy results from ANNEXA-I provide clinical evidence of effective hemostasis with andexanet — supporting an application for full approval.
- Treatment with andexanet resulted in a statistically significant and clinically relevant improvement in effective hemostasis at 12 hours compared to usual care (adjusted absolute treatment difference: 13.4% [95% CI: 4.6%, 22.2]).
- This benefit was consistently observed across sensitivity analyses and the exploratory patient subgroup analyses for the primary endpoint.
- Andexanet provided numerical improvements in all aspects of effective hemostasis, including hematoma expansion, neurologic function, and use of rescue therapy.
- Andexanet was superior to usual care in reducing anti-FXa activity from baseline to nadir during the first 2 hours post-randomization, with a 94% median reduction in the andexanet group compared to a 27% median reduction in the usual care group.

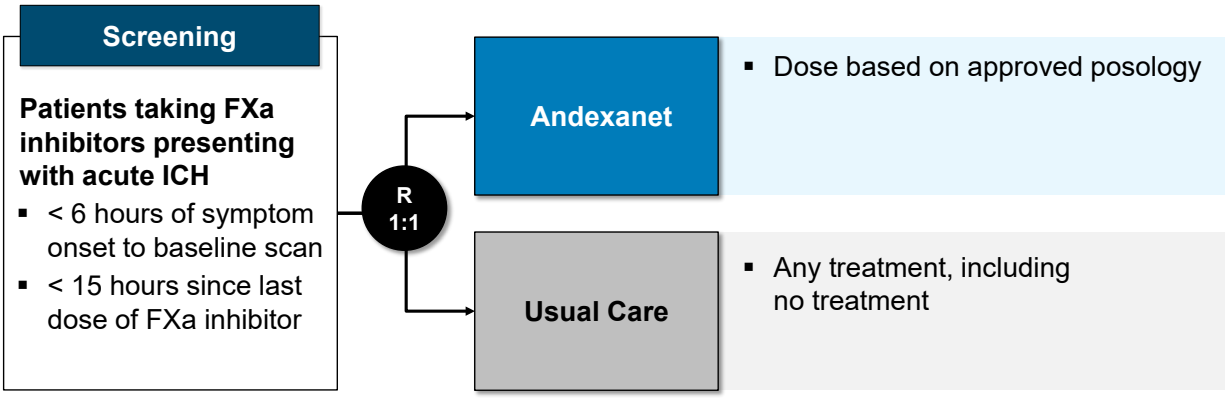
6.1 ANNEXA-I Study Design

6.1.1 Overview

ANNEXA-I was a randomized, open-label, multicenter, clinical Phase 4 study investigating the use of andexanet in acute ICrH in patients receiving a direct oral FXa inhibitor. ANNEXA-I was designed to test the hypothesis that andexanet is superior to usual care in achieving effective hemostasis at 12 hours post-randomization.

Eligible patients were randomized 1:1 to andexanet or usual care, stratified by the site's intended-usual-care-agent response and also the time from symptom onset to baseline scan (Figure 17).

Figure 17: Annexa-I Study Design



- Imaging performed at baseline and 12 hours following randomization
- Neurologic assessments (NIHSS) performed at baseline, 2, 3, 6, 12, 24, and 72 hours
- Safety follow-up for 30 days after treatment

FXa: activated factor X; ICH: intracranial hemorrhage; NIHSS: National Institutes of Health Stroke Scale; R: randomization.

6.1.2 Treatment

Patients randomized to the andexanet group received one of 2 doses of andexanet based on the specific FXa inhibitor and dose taken and timing of the most recent dose (see Table 6).

According to the prescribing information in the label, the andexanet dosing regimens included:

- Low dose: 400 mg IV bolus followed by a continuous infusion of 480 mg at 4 mg/min for approximately 120 minutes
- High dose: 800 mg IV bolus followed by a continuous infusion of 960 mg at 8 mg/min for approximately 120 minutes

At the time of study initiation, no pharmacological treatment other than andexanet was approved in life-threatening or uncontrolled bleeding in patients receiving a direct oral FXa inhibitor. Therefore, usual care was selected as an appropriate comparator. Usual care consisted of any treatment(s) (including no treatment) other than andexanet initiated within 3 hours post-randomization.

6.1.3 Enrollment Criteria

Key inclusion criteria included:

- Acute intracerebral bleeding episode[1]
  - CT-scan or MRI-confirmed bleeding < 2 hours prior to randomization
- Received FXa inhibitor with last dose ≤ 15 hours prior to randomization
  - Apixaban, rivaroxaban, edoxaban
  - More than 15 hours prior to randomization or unknown time of last dose if documented anti-FXa activity is > 100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban or edoxaban)
- Bleeding symptom onset < 6 hours prior to baseline imaging

Key exclusion criteria included:

- GCS score < 7, NIHSS score > 35, or hematoma volume < 0.5 or > 60 mL
- Planned surgery within 12 hours (except minimally invasive procedures)
- Expected survival < one month
- Recent history of diagnosed thrombotic event (within 2 weeks)
- Receipt of warfarin, dabigatran, PCC, recombinant activated factor VII (rFVIIa) or anti-FXa inhibitor coagulant complex, FFP or whole blood within 7 days prior to consent

6.1.4 Endpoints

6.1.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint in ANNEXA-I was effective hemostasis 12 hours post-randomization. For a patient to have excellent or good hemostatic efficacy, all the following criteria were to be met:

- No greater than 35% increase from baseline in hematoma volume compared with baseline on repeat CT scan or MRI at 12 hours post-randomization as determined by a blinded EAC
- ≤ 6-point change in NIHSS score from the baseline score at 12 hours post-randomization
- Had not received rescue therapy between 3- and 12-hours post-randomization

[1] Eligibility criteria were updated in protocol amendment 1 to limit enrollment to patients with intracerebral hemorrhage to increase the homogeneity of the study population and to clarify eligible hematoma blood volume.

CT/MRI-based volumetric measurement is considered the most direct way to evaluate hemostatic efficacy. An independent imaging core laboratory was used in this study to quantify hematoma size objectively of clinical status in the acute phase was captured by the NIHSS, and the use of rescue therapies provided information about durability of hemostasis. Adjudication of hemostatic efficacy was hence based on a combination of imaging and clinical findings.

6.1.4.2 Secondary Efficacy Endpoint

The secondary efficacy endpoint in ANNEXA-I was percent change from baseline to nadir in anti-FXa activity during the first 2 hours post-randomization.

6.1.4.3 Additional Efficacy Endpoint

An additional efficacy objective was to assess the relationship between anti-FXa activity and the achievement of hemostatic efficacy.

6.1.4.4 Safety Endpoints

Safety endpoints included the following:

- Occurrence of thrombotic event, confirmed by adjudication, through 30 days post-randomization
- Mortality endpoints:
    - In-hospital mortality (during index hospitalization; all-cause, CV, and bleeding)
    - 30-day all-cause, CV, and bleeding-related mortality (defined as death within 72 hours of randomization, and not associated with the occurrence of an identified thrombotic event)
- Proportion of patients with invasive intracranial procedures performed post- randomization to manage the intracranial hematoma and/or its complications
- Hospitalization endpoints:
    - Length of initial hospitalization for primary bleeding event
    - Total time admitted to the intensive care unit during the initial hospitalization
    - Proportion of re-hospitalizations, including total number of re-hospitalizations and total days re-hospitalized, at 30 days post-randomization

6.1.5 Endpoint Adjudication

The primary efficacy outcome was adjudicated by a blinded, independent EAC that comprised of experts in the fields of neurology, cardiology, and/or thrombosis, and were

selected based on their clinical expertise and previous adjudication experience. The EAC also adjudicated all potential thrombotic events and deaths.

6.1.6 Statistical Methods

6.1.6.1 Sample Size

Results from the Phase 3b/4 single arm, open-label andexanet study ANNEXA-4 (as of 30 June 2020) showed a rate of effective hemostasis of 79% (95% CI: 74%, 84%) based on evaluable patients with ICrH. The rate of effective hemostasis was 80% (95% CI: 75%, 84%) based on 340 efficacy-evaluable patients with all types of bleeding.

Based on these results, it was assumed that the rate of effective hemostasis in this study would be 70% and 80% for patients treated with usual care and andexanet, respectively. The 10% absolute difference represented a 33% risk reduction of not achieving effective hemostasis by andexanet as compared to usual care, which was considered clinically meaningful. After accounting for early discontinuation rate and one interim analysis, it was estimated that a total sample size of approximately 900 patients (ie, 450 patients per group) would have approximately 90% power to detect a 10% absolute difference in the rate of effective hemostasis at a 0.05 2-sided significance level.

6.1.6.2 Efficacy Analysis Populations

All efficacy endpoints were analyzed using the intent to treat (ITT) Set, including all randomized patients according to the randomized treatment.

The ITT Set for efficacy analyses based on the first data cut-off is referred to as “ITT Set, Primary Efficacy Population”; these patients were included in the interim analysis. The ITT Set based on the second data cut-off is referred to as “ITT Set, Extended Population”.

6.1.6.3 Endpoint Analyses

The primary and secondary endpoints were tested in a hierarchical sequence in the primary efficacy population. All efficacy hypothesis tests were 2-sided and performed at the significance level 0.0310 at the interim. If the interim p-value was < 0.0310 for comparing andexanet and usual care in the primary endpoint analysis, the DSMB could recommend stopping the study. Had the study not been stopped at the interim analysis, the final analysis would have been performed at a significance level of 0.0277 to preserve the overall type I error at 0.05.

The analysis of the primary efficacy endpoint was performed using a Cochran-Mantel Haenszel test stratified by time from symptom onset to the baseline imaging scan (< 180 minutes vs ≥ 180 minutes). Patients assessed as non-evaluable (either due to clinical or administrative reasons) were included in the analysis as having non-effective hemostasis. The weighted mean difference in the proportion of patients with effective hemostasis, its 95% CI, and the p-value were provided.

The analysis of the secondary efficacy endpoint was performed using an ANCOVA on the ranked percent change in anti-FXa activity from baseline to nadir 2 hours post-randomization, adjusted for covariates of time from symptom onset to the baseline imaging scan (< 180 minutes vs ≥ 180 minutes), and baseline anti-FXa activity.

Interim Analysis

There were 2 data cut-off points in ANNEXA-I. The first data cut off was for the planned interim analysis of the primary efficacy endpoint by the independent DSMB, after approximately 50% of the anticipated patients had been adjudicated for effective hemostasis. The DSMB recommended to stop the study based on the interim analysis results. As prespecified, the first data cut-off was used for confirmatory analyses of efficacy endpoints (primary efficacy population) following the DSMB recommendation to stop the study.

Enrollment of patients continued without interruption from the first data cut-off until the stop decision was communicated and recruitment was closed. The second data cut-off captured the data from all patients who participated in the study (extended population) and forms the basis for the safety analyses along with sensitivity analyses of the efficacy endpoints.

6.2 ANNEXA-I Patient Population

6.2.1 Disposition

In the primary efficacy population, 452 patients were enrolled and randomized: 224 patients to the andexanet group and 228 to the usual care group (Table 13). The extended population included a total of 530 patients, 263 in the andexanet group and 276 in the usual care group.

The proportion of patients who discontinued from the study was balanced between the treatment groups. The most common reason for discontinuation from study was death (Table 13).

Table 13: ANNEXA-I Patient Disposition

	Primary Efficacy Population		Extended Population	
Disposition, n (%)	**Andexanet**	**Usual Care**	**Andexanet**	**Usual Care**
Randomized (N)	224	228	263	267
Completed Study	160 (71.4)	167 (73.2)[b]	180 (68.4)	193 (72.3)[b]
Discontinued Study	64 (28.6)	61 (26.8)	83 (31.6)	74 (27.7)
Died	56 (25.0)[a]	59 (25.9)	75 (28.5)[a]	69 (25.8)
Withdrawal by patient	5 (2.2)	1 (0.4)	5 (1.9)	3 (1.1)
Other	3 (1.3)	1 (0.4)	3 (1.1)	2 (0.7)

a. Includes one patient who did not receive treatment, excluded from the Safety Set.
b. Includes one patient who died.

6.2.2 Treatment Received

In ANNEXA-I, the mean time from baseline scan to randomization was approximately one hour and baseline scan to treatment was approximately 1.5 hours (Table 14).

Table 14: ANNEXA-I Time to Treatment (ITT Set, Primary Efficacy Population)

	Andexanet (N=224)	Usual care (N=228)
Time from symptom onset to baseline imaging scan (minutes)		
Mean (SD)	180.28 (127.70)	177.04 (130.41)
Median (Min, Max)	137.00 (11.0, 683.0)	146.00 (16.0, 715.0)
< 180 minutes	137 (61.2)	143 (62.7)
≥ 180 minutes	87 (38.8)	85 (37.3)
Time from symptom onset to treatment (hours)		
n	221	228
Mean (SD)	4.55 (2.09)	4.64 (2.22)
Median (Min, Max)	4.00 (1.3, 12.6)	4.13 (1.2, 13.5)
Time from baseline imaging scan to treatment (hours)		
n	221	228
Mean (SD)	1.55 (0.65)	1.69 (0.74)
Median (Min, Max)	1.47 (0.2, 4.5)	1.65 (0.2, 4.0)

SD: standard deviation.
Percentages are based on number of patients with non-missing values in each treatment group.

In the andexanet group, patients were eligible for one of 2 dosing regimens based on FXa inhibitor and amount and timing of the most recent dose: 78.1% of patients received the low dose regimen and 20.1% of patients the high dose regimen (1.8% were randomized to andexanet but were not treated with andexanet).

In the usual care group, 84.6% of patients were treated with PCC, 15.4% of patients did not receive PCCs (platelets, packed red blood cells, or other therapies were allowed).

6.2.2.1 Invasive Intracranial Procedures

Overall, 17 (6.5%) patients in the andexanet group and 23 (8.7%) in the usual care group had at least one invasive intracranial procedure. The most common invasive intracranial procedure in both treatment groups was burr hole for implanting ventricular catheter.

6.2.3 Baseline Demographics

The demographic characteristics of the patients were balanced between treatment groups (Table 15). In the primary efficacy population, the median age was 80 years, and the population was predominantly White; 54.2% of patients were male.

Table 15: ANNEXA-I Demographic Characteristics (ITT Set, Primary Efficacy Population)

Characteristic	Andexanet (N=224)	Usual Care (N=228)
Age (years)		
Mean (SD)	78.9 (8.52)	78.9 (8.48)
Median (IQR)	80.0 (11.0)	80.0 (11.0)
Min, Max	48, 96	42, 96
Age group (years), n (%)		
< 65	13 (5.8)	15 (6.6)
65–74	45 (20.1)	46 (20.2)
≥ 75	166 (74.1)	167 (73.2)
Sex, n (%)		
Male	130 (58.0)	115 (50.4)
Female	94 (42.0)	113 (49.6)
Race, n (%)	217	227
White	202 (93.1)	213 (93.8)
Black or AfricanAmerican	5 (2.3)	3 (1.3)
Asian	3 (1.4)	3 (1.3)
Other	7 (3.2)	8 (3.5)
Missing	7	1
Ethnicity, n (%)		
Hispanic or Latino	14 (6.3)	11 (4.8)
Not Hispanic or Latino	191 (85.3)	205 (89.9)
Not Reported	14 (6.3)	11 (4.8)
Unknown	5 (2.2)	1 (0.4)
Region, n (%)		
Europe[a]	198 (88.4)	203 (89.0)
North America	26 (11.6)	25 (11.0)

IQR: interquartile range; ITT: intent to treat; SD: standard deviation.
a. Israel is counted as Europe.

6.2.4 Baseline Characteristics

The baseline characteristics were balanced between treatment groups (Table 16). The most common FXa inhibitor was apixaban in both groups. In the primary efficacy

population, the most common indications for FXa inhibitors were atrial fibrillation, venous thromboembolism prevention, and venous thromboembolism treatment.

Table 16: ANNEXA-I Baseline Characteristics (ITT Set, Primary Efficacy Population)

Category	Andexanet (N=224)	Usual Care (N=228)
FXa inhibitor, n (%) [a]		
Apixaban	140 (62.5)	135 (59.2)
Rivaroxaban	64 (28.6)	65 (28.5)
Edoxaban	20 (8.9)	25 (11.0)
Indication for FXa inhibitor, n (%)		
Atrial fibrillation	194 (86.6)	189 (82.9)
Venous thromboembolism prevention	10 (4.5)	14 (6.1)
Venous thromboembolism treatment	6 (2.7)	14 (6.1)
Arterial thromboembolism	5 (2.2)	1 (0.4)
Atrial flutter	2 (0.9)	4 (1.8)
Acute coronary syndrome	1 (0.4)	0
Peripheral arterial disease	1 (0.4)	1 (0.4)
Chronic coronary disease	1 (0.4)	0
Prosthetic valve	1 (0.4)	2 (0.9)
Heart failure	0	1 (0.4)
Other	3 (1.3)	2 (0.9)

FXa: activated factor X; ITT: intent to treat.
a. Three patients received enoxaparin under protocol amendment 2.
Percentages are based on number of patients with non-missing values in each treatment group.

The most common bleeding event location was intracerebral hemorrhage in both groups, and the mechanism of injury was spontaneous for the majority of bleeding events (Table 17). The median hematoma volume at baseline was 10.61 mL in the andexanet group and 9.04 mL in the usual care group.

Table 17: ANNEXA-I Baseline Characteristics of Initial Bleed Event (ITT Set, Primary Efficacy Population)

Baseline characteristic	Andexanet (N=224)	Usual Care (N=228)
Primary bleeding location, n (%)		
Intracerebral	198 (88.8)	214 (94.3)
Subdural	13 (5.8)	4 (1.8)
Subarachnoid	9 (4.0)	8 (3.5)
Intraventricular	3 (1.3)	1 (0.4)
Missing	1	1
Mechanism of injury, n (%)		
Spontaneous	198 (88.4)	195 (85.5)
Trauma	26 (11.6)	33 (14.5)
Average hematoma volume of baseline CT/MRI (mL) from core laboratory		
n	224	227
Mean (SD)	17.50 (20.26)	16.76 (21.43)
Median (Min, Max)	10.61 (0.0, 132.1)	9.04 (0.1, 168.7)
< 30	180 (80.4)	192 (84.6)
≥ 30 and < 60	32 (14.3)	26 (11.5)
≥ 60	12 (5.4)	9 (4.0)
ICH score		
Mean (SD)	1.4 (1.04)	1.3 (1.06)
Median (Min, Max)	1.0 (0, 4)	1.0 (0, 5)
< 3	195 (87.1)	199 (87.3)
≥ 3	29 (12.9)	29 (12.7)

CT: computed tomography; ICH: intracerebral hemorrhage; ITT: intent to treat; MRI: magnetic resonance imaging; SD: standard deviation.
Percentages are based on number of patients with non-missing values in each treatment group.

The medical history of the patients was generally balanced between treatment groups and was consistent with the typical comorbidities seen in this patient population (Table 18).

Table 18: Medical History (Safety Set, Primary Efficacy Population)

System Organ Class Preferred Term, n (%)	Andexanet (N=223)	Usual Care (N=226)
Cardiac disorders	209 (93.7)	209 (92.5)
Atrial fibrillation	200 (89.7)	191 (84.5)
Cardiac failure congestive	30 (13.5)	45 (19.9)
Myocardial infarction	23 (10.3)	32 (14.2)
Angina pectoris	15 (6.7)	12 (5.3)
Coronary artery disease	12 (5.4)	21 (9.3)
Vascular disorders	194 (87.0)	186 (82.3)
Hypertension	183 (82.1)	180 (79.6)
Deep vein thrombosis	18 (8.1)	22 (9.7)
Metabolism and nutrition disorders	140 (62.8)	131 (58.0)
Diabetes mellitus	82 (36.8)	58 (25.7)
Hyperlipidaemia	34 (15.2)	32 (14.2)
Dyslipidaemia	24 (10.8)	40 (17.7)
Hypercholesterolaemia	24 (10.8)	32 (14.2)
Nervous system disorders	96 (43.0)	105 (46.5)
Cerebrovascular accident	46 (20.6)	48 (21.2)
Transient ischemic attack	21 (9.4)	22 (9.7)
Respiratory, thoracic and mediastinal disorders	61 (27.4)	54 (23.9)
Chronic obstructive pulmonary disease	19 (8.5)	17 (7.5)
Pulmonary embolism	17 (7.6)	20 (8.8)
Renal and urinary disorders	58 (26.0)	38 (16.8)
Chronic kidney disease	34 (15.2)	27 (11.9)
Endocrine disorders	48 (21.5)	52 (23.0)
Hypothyroidism	33 (14.8)	40 (17.7)
Blood and lymphatic system disorders	20 (9.0)	23 (10.2)
Anaemia	10 (4.5)	12 (5.3)

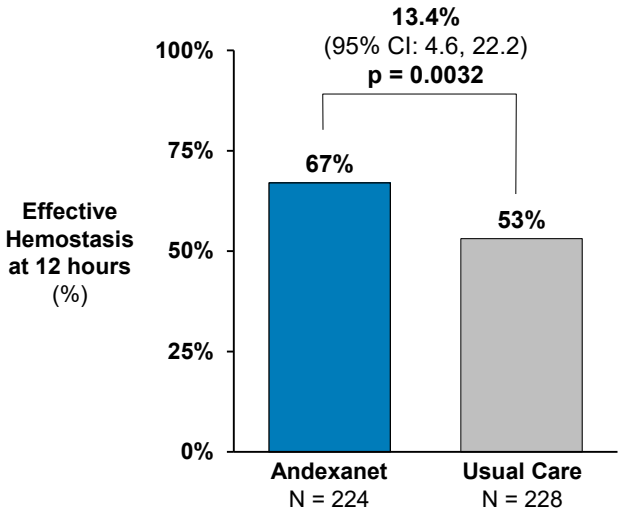
6.3 ANNEXA-I Efficacy Results

6.3.1 Primary Endpoint

6.3.1.1 Proportion of Patients with Effective Hemostasis 12 Hours Post-Randomization as Determined by the Blinded EAC

Compared to usual care, treatment with andexanet had a statistically significant and clinically relevant benefit in achieving effective hemostasis 12 hours post-randomization in acute ICrH in patients receiving a direct oral FXa inhibitor (Figure 18). The adjusted absolute treatment difference was 13.4% (95% CI: 4.6%, 22.2).

Figure 18: ANNEXA-I Primary Efficacy Results: Hemostatic Efficacy (ITT Set, Primary Efficacy Population)

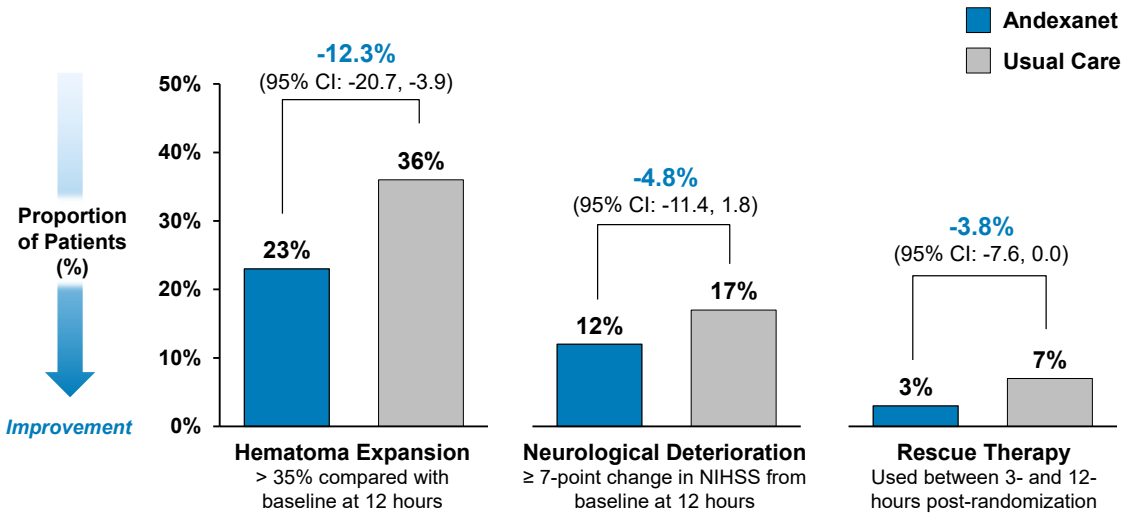


CI: confidence interval; ITT: intent to treat.
Note: The p-value, proportion difference and 95% CI are from Cochran-Mantel Haenszel test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

6.3.1.2 Components of Hemostatic Efficacy

Numerical improvements in the andexanet group compared to the usual care group were observed for each of the 3 components assessed in the primary endpoint (Figure 19). Note, the 3 components are not mutually exclusive and therefore cannot simply be added up to reach the primary endpoint.

Figure 19: ANNEXA-I Primary Efficacy Results by Component (ITT Set, Primary Efficacy Population)

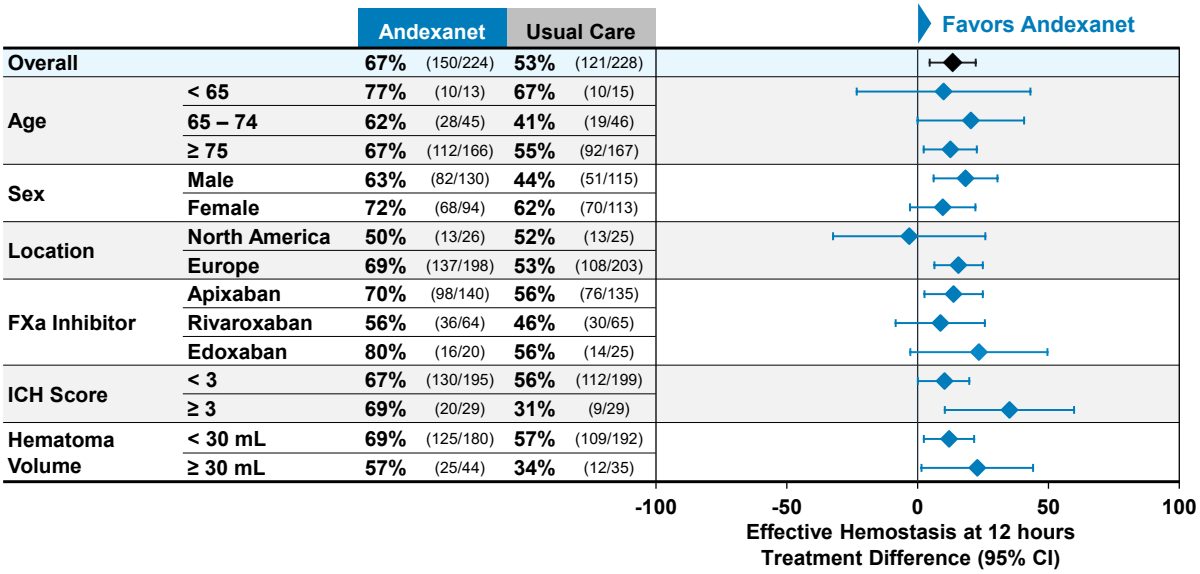


CI: confidence interval; ITT: intent to treat; NIHSS: National Institutes of Health Stroke Scale.
Note: The p-values, proportion differences and 95% CIs are from Cochran-Mantel Haenszel test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

6.3.1.3 Subgroup Analyses

The treatment effect was generally consistent across pre-defined subgroups based on demographic and important baseline characteristics, supporting the primary endpoint results (Figure 20).

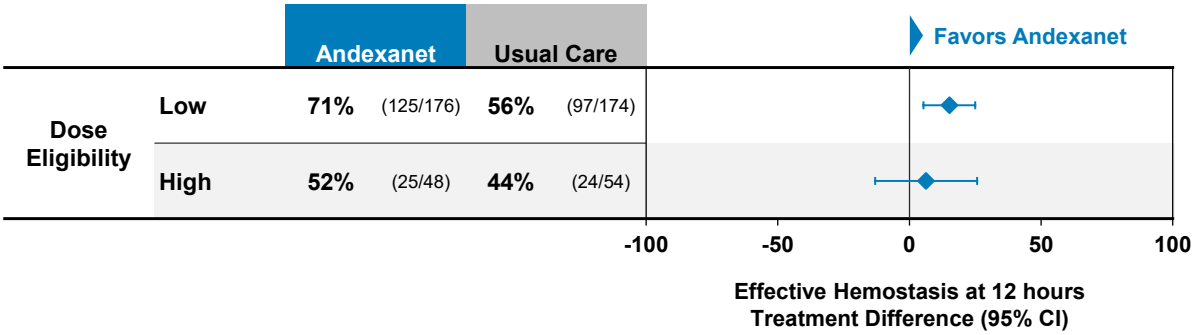
Figure 20: ANNEXA-I Primary Endpoint Key Prespecified Subgroup Analyses (ITT Set, Primary Efficacy Population)



CI: confidence interval; FXa: activated factor X; ICH: intracerebral hemorrhage.

An additional analysis comparing patients eligible for the high and low dose of andexanet favored andexanet for both doses. Doses were determined by the treatment algorithm and are thus non-randomized groups with different baseline characteristics. (Figure 21).

Figure 21: ANNEXA-I Primary Endpoint Subgroup Analyses by Dose Eligibility (ITT Set, Primary Efficacy Population)



CI: confidence interval.

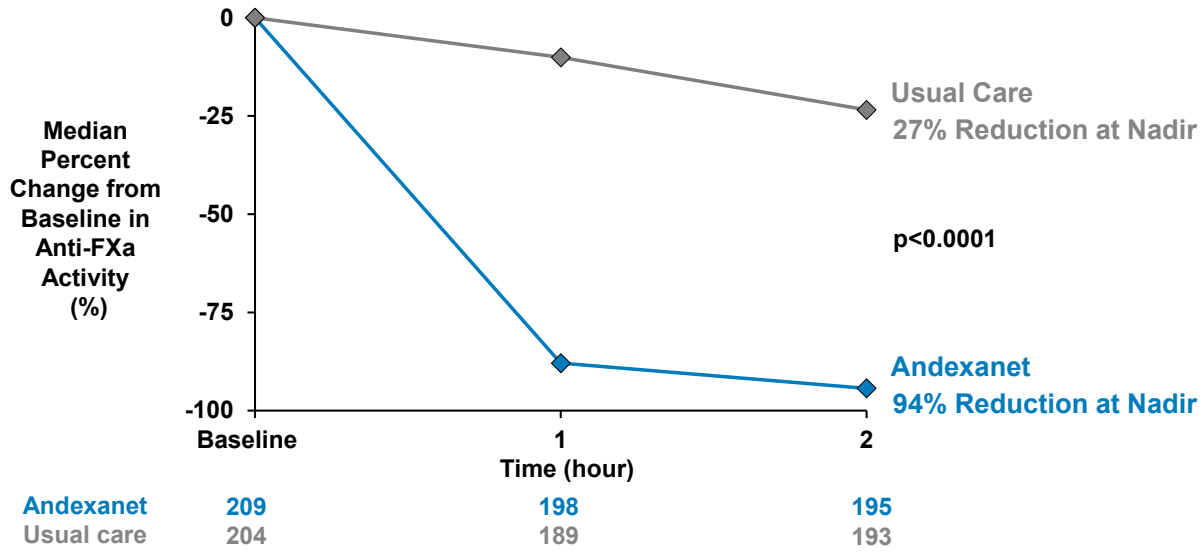
6.3.2 Secondary Endpoint

6.3.2.1 Change in Anti-FXa Activity from Baseline to Nadir at 2 Hours Post-Randomization

Andexanet was superior to usual care in reducing anti-FXa activity from baseline to nadir during the first 2 hours post-randomization in acute ICrH in patients receiving a direct oral FXa inhibitor (-94.4% median reduction in the andexanet group, -27.5% median reduction in the usual care group, $p < 0.0001$). Percent change in anti-FXa activity from Baseline through 2 hours post-randomization is presented in Figure 22.

The reduction in the andexanet group corresponds to actual values of anti-FXa activity which are well below 30 ng/mL, while in the usual care group patients could be considered still anticoagulated by their anti-FXa inhibitor at an anti-FXa activity >100 ng/mL (see Figure 5)

Figure 22: Percent Change from Baseline in Anti-FXa Activity by Treatment in Patients Overall (ITT Set, Primary Efficacy Population)



FXa: activated factor X; ITT: intent to treat.

6.3.3 Additional Endpoints

6.3.3.1 Relationship Between Effective Hemostasis and Anti-FXa Activity

6.3.3.1.1 Pre-Specified Analysis

Overall, in the pre-specified analysis, there was a weak relationship between the hemostatic efficacy and percentage change in anti-FXa activity (OR: 0.9988, 95% CI [0.9952, 1.0024], area under the receiver operating characteristic curve: 0.56, 95% CI [0.51, 0.62]; Table 19).

Anti-FXa activity is an established biomarker for anticoagulation status in patients treated with an FXa inhibitor since it reflects exposure and was studied in association with stopping life-threatening or uncontrolled bleeding in the ANNEXA-4 study (Milling et al 2023). The effective and consistent reduction and the low variability in response between patients in anti-FXa activity after treatment with andexanet, with most patients having reductions > 90%, makes it difficult to show a strong predictive value of reduction in anti-FXa activity on the primary endpoint based on this biomarker alone.

Table 19: Relationship between Effective Hemostasis with Anti-FXa Activity (ITT Set, Primary Efficacy Population)

Change from Baseline	Odds ratio for anti-FXa activity (95% CI)	AUC for anti-FXa activity (95% CI)
Percent change from baseline in anti-FXa activity	0.9988 (0.9952, 1.0024)	0.56 (0.51, 0.62)
Absolute change from baseline in anti-FXa activity	0.9982 (0.9942, 1.0021)	0.49 (0.43, 0.55)

CI confidence interval; FXa: activated factor X; ITT: intent to treat.

6.3.3.1.2 Post hoc Analysis Adjusting for Baseline Factors

In the ANNEXA-I study, the assessment of hemostatic efficacy was based on 3 components, including hematoma expansion. Several clinical predictors of hematoma expansion have been identified that a reversal agent is unable to change (Al-Shahi Salman et al 2018; Morotti et al 2023). These predictors include time from symptom onset to presentation, baseline hematoma volume, blood pressure, as well as time from the last dose of FXa inhibitor. Heterogeneity in these clinical predictors in the trial provides a limitation and confounding to the pre-specified univariate analysis between change in anti-FXa activity and hematoma expansion.

A post hoc analysis of the association between reduction in anti-FXa activity and hemostatic efficacy was performed by adjusting for different clinical predictors available at baseline (Table 20). These results demonstrate that a longer time between symptom onset and treatment start, lower baseline diastolic blood pressure, lower baseline anti-FXa level, and a smaller baseline hematoma volume are associated with effective hemostasis at 12 hours. The importance of these clinical predictors is evident in achieving hemostatic efficacy and may, in part, explain the weak relationship between hemostatic efficacy and reduction in anti-FXa activity observed in ANNEXA-I. There was a clear association between reduction in anti-FXa activity and effective hemostasis after adjusting for those predictors (OR: 1.495, 95% CI: 1.100, 2.033 per 100 ng/ml reduction).

Table 20: Association between Effective Hemostasis and Reduction in Anti-FXa Activity, Baseline Anti-FXa Activity, Hematoma Volume, Diastolic Blood Pressure, and Time from Symptom Onset to Treatment (ITT Set, Extended Population)

Variable	Odds Ratio	95% CI
Reduction in anti-FXa activity from baseline to nadir (per 100 ng/mL reduction)	1.495	(1.100, 2.033)
Baseline anti-FXa activity (per 100 ng/mL)	0.575	(0.430, 0.768)
Baseline hematoma (per 10 mL)	0.796	(0.720, 0.879)
Baseline diastolic blood pressure (per 10 mmHg)	0.879	(0.791, 0.976)
Time from symptom onset to treatment (per hour)	1.271	(1.132, 1.428)

CI: confidence interval; FXa: activated factor X; ITT: intent to treat.
Odds ratios, 95% CIs, and p-values are estimated from a logistic regression model with reduction in anti-FXa activity, baseline anti-FXa activity, hematoma volume, diastolic blood pressure, and time from symptom onset to treatment as covariates.

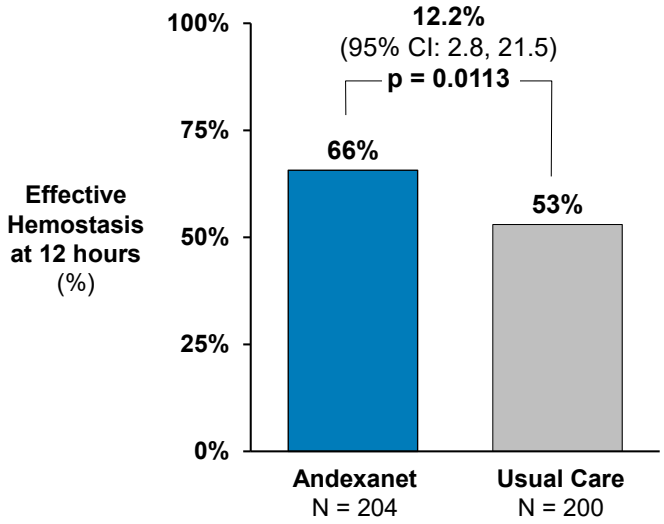
6.3.4 Sensitivity Analyses – Participants Who Received Apixaban or Rivaroxaban

To align with the indication for use in the US and at the request of FDA, sensitivity analyses of all prespecified analysis were performed to evaluate the benefit-risk of andexanet in the subset of patients receiving apixaban or rivaroxaban. The results for patients who received apixaban or rivaroxaban were observed to be consistent with those for the overall ANNEXA-I study population.

6.3.4.1 Proportion of Patients with Effective Hemostasis 12 Hours Post-Randomization as Determined by the Blinded EAC – Participants Who Received Apixaban or Rivaroxaban

A total of 65.7% of patients in the andexanet group compared to 53.0% of patients in the usual care group achieved the primary endpoint, resulting in an adjusted absolute treatment difference of 12.2% (p=0.0113; Figure 23).

Figure 23: ANNEXA-I Hemostatic Efficacy at 12 Hours in Patients Receiving Apixaban and Rivaroxaban (ITT Set, Primary Efficacy Population)

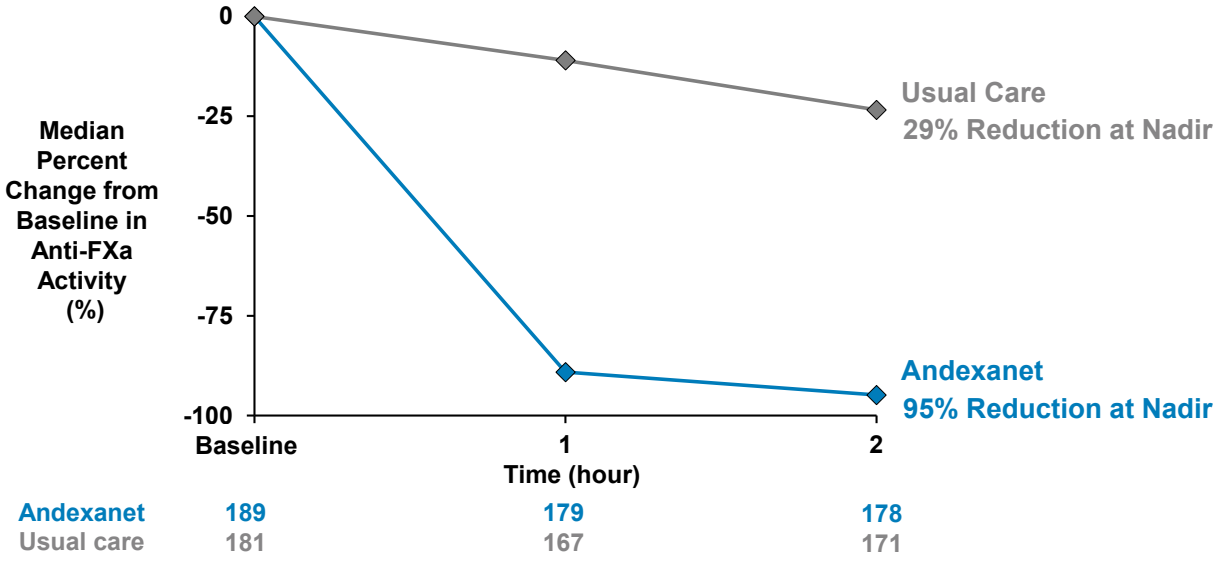


CI: confidence interval; ITT: intent to treat.
Note: The p-value, proportion difference and 95% CI are from Cochran-Mantel Haenszel test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

6.3.4.2 Change in Anti-FXa Activity from Baseline to Nadir at 2 Hours Post-Randomization – Participants Who Received Apixaban or Rivaroxaban

The median reduction in anti-FXa activity from baseline to nadir during the first 2 hours post-randomization in acute ICrH in patients receiving a direct oral FXa inhibitor was -95.0% in the andexanet group and -29.4% in the usual care group. Percent change in anti-FXa activity from baseline through 2 hours post-randomization for participants who received apixaban or rivaroxaban is shown in Figure 24.

Figure 24: Percent Change in Anti-FXa Activity from Baseline to 2 Hours Post-Randomization in Participants Who Received Apixaban or Rivaroxaban (ITT Set, Primary Efficacy Population)



FXa: activated factor X; ITT: intent to treat.

6.4 Efficacy Conclusions

The efficacy results from ANNEXA-I provide clinical evidence of effective hemostasis with andexanet supporting an application for full approval. Treatment with andexanet resulted in a statistically significant and clinically relevant improvement in effective hemostasis at 12 hours compared to usual care. This benefit was consistently observed across sensitivity analyses and the exploratory patient subgroup analyses for the primary endpoint.

When assessing each component of the primary endpoint, andexanet provided numerical improvements in all aspects of effective hemostasis, including hematoma expansion, neurologic function, and use of rescue therapy. In addition, andexanet resulted in a significant reduction in anti-FXa activity compared with usual care.

Importantly, ANNEXA-I confirms the findings from the single-armed study ANNEXA-4 and supports the benefit of andexanet in patients who experience life-threatening or uncontrolled bleeding in emergency situations.

7 ANNEXA-I CLINICAL SAFETY

Summary

- The overall safety profile of andexanet in the ANNEXA-I population was consistent with the known safety profile of andexanet and no new safety signals were identified.
- The proportion of patients with TEAEs was balanced between treatment groups: 85.1% of patients in the andexanet group vs 82.6% in the usual care group. The most common TEAEs in the andexanet group were urinary tract infection, pneumonia, and hypokalemia.
- The proportion of patients with TESAEs was higher in the andexanet group (45.8%) than in the usual care group (36.2%).
- The 30-day overall mortality rate was 28.2% in the andexanet group and 26.4% in the usual care group.
- The frequency of patients with thrombotic events was higher in the andexanet group (10.3%) than in the usual care group (5.7%); however, the rate was consistent with the rate of thrombotic events seen in patients with acute major bleeding who participated in ANNEXA-4 (10.5%) and in line with the information provided in the current USPI.
- In patients who received at least one dose of anticoagulant medication as a prophylactic measure, the rate of thrombotic events was low and similar between treatment groups (4.9% and 4.8%).

7.1 Safety Population

In the ANNEXA-I study, a total of 527 patients received study drug: 262 patients in the andexanet group and 265 patients in the usual care group. These 527 patients served as the primary safety population for evaluating andexanet. Three patients randomized to the andexanet group did not receive any treatment and were not included in the safety population.

7.2 Treatment Exposure

A total of 203 patients received the low dose of andexanet, and 59 received the high dose. The mean duration of the initial bolus was 15.2 minutes for the low dose and 29.7 minutes for the high dose. The mean duration of the follow-up infusion was approximately 118 minutes, as expected per the prescribing information.

Of the 265 patients in the usual care group, 230 patients were treated with PCC, 2 patients received other treatments, and 33 patients received no hemostatic treatment (platelets and packed red blood cells were allowed).

7.3 Overview of Adverse Events

Overall, the proportions of patients with AEs were balanced between treatment groups (Table 21). The proportion of patients with SAEs was higher in the andexanet group compared with the usual care group. Deaths due to AEs occurred in 64 patients (24.4%) in the andexanet group and 54 (20.4%) in the usual care group. Due to the study design, and as stated in the protocol, all deaths were not reported as an AE (disease progression was not reported as an AE; see Section 7.6). All-cause mortality through 30 days was 28.2% in the andexanet group and 26.4% in the usual care group.

The overall safety profile of andexanet compared to usual care was similar in the subset of patients receiving apixaban and rivaroxaban. Thus, to provide the most robust assessment of andexanet safety, the safety discussion will focus on the overall primary safety population.

Table 21: Overview of Adverse Events (Safety Set)

	Primary Safety Population		Apixaban and Rivaroxaban Safety Population	
Patients, n (%)	**Andexanet (N=262)**	**Usual Care (N=265)**	**Andexanet (N=239)**	**Usual Care (N=232)**
TEAEs	223 (85.1)	219 (82.6)	205 (85.8)	190 (81.9)
TESAE	120 (45.8)	96 (36.2)	111 (46.4)	86 (37.1)
TEAE leading to withdrawal of study drug	0	0	0	0
TEAE leading to interruption of study drug	1 (0.4)	0	1 (0.4)	0
TEAE leading to death	64 (24.4)	54 (20.4)	59 (24.7)	49 (21.1)
All-cause mortality through 30 days	74 (28.2)	70 (26.4)	67 (28.0)	61 (26.3)

AE(s): adverse event(s); SAE(s): serious adverse event(s); TEAE(s): treatment-emergent adverse event(s); TESAE: treatment-emergent serious adverse event.
Note: In accordance with the study protocol, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurred within the first 12 hours post-randomization were not regarded as an AE or SAE except when there was evidence suggesting a causal relationship between the drug and the event. Thus, death due to disease progression was not reported with an SAE or AE leading to death.

7.4 Common Adverse Events

Overall, the proportions of patients with AEs were balanced between treatment groups (Table 22). The most frequently reported preferred terms in both treatment groups were urinary tract infection, pneumonia, and hypokalemia.

The frequency of ischemic stroke was higher in the andexanet group than in the usual care group; these events are further described in Section 7.7.

Table 22: Adverse Events with Incidence Rate ≥ 5% (Safety Set)

Preferred Term, n (%)	Andexanet (N=262)	Usual Care (N=265)
Any AE	223 (85.1)	219 (82.6)
Urinary tract infection	55 (21.0)	45 (17.0)
Pneumonia	42 (16.0)	40 (15.1)
Hypokalaemia	40 (15.3)	28 (10.6)
Constipation	39 (14.9)	25 (9.4)
Pneumonia aspiration	33 (12.6)	23 (8.7)
Pyrexia	24 (9.2)	22 (8.3)
Headache	24 (9.2)	19 (7.2)
Nausea	23 (8.8)	17 (6.4)
Delirium	21 (8.0)	29 (10.9)
Hypertension	18 (6.9)	19 (7.2)
Ischemic stroke	15 (5.7)	2 (0.8)
Insomnia	14 (5.3)	9 (3.4)
Vomiting	9 (3.4)	14 (5.3)

AE: adverse event.

7.5 Serious Adverse Events

The proportion of patients with reported SAEs was higher in the andexanet group than in the usual care group (Table 23).

The most frequently reported SAEs were pneumonia, pneumonia aspiration, and ischemic stroke in the andexanet group and pneumonia, hemorrhage intracranial, and cerebral hemorrhage in the usual care group.

Table 23: Serious Adverse Events with Incidence Rate ≥ 1% (Safety Set)

System Organ Class Preferred Term	Andexanet (N=262) n (%)	Usual Care (N=265) n (%)
Any TESAE	120 (45.8)	96 (36.2)
Nervous system disorders	49 (18.7)	51 (19.2)
Haemorrhage intracranial	8 (3.1)	11 (4.2)
Cerebral haemorrhage	7 (2.7)	11 (4.2)
Ischaemic stroke	13 (5.0)	2 (0.8)
Hydrocephalus	7 (2.7)	4 (1.5)
Neurological decompensation	2 (0.8)	7 (2.6)
Cerebral haematoma	3 (1.1)	5 (1.9)
Infections and infestations	43 (16.4)	28 (10.6)
Pneumonia	14 (5.3)	16 (6.0)
Pneumonia aspiration	14 (5.3)	7 (2.6)
Sepsis	6 (2.3)	2 (0.8)
Urinary tract infection	4 (1.5)	1 (0.4)
Cardiac disorders	22 (8.4)	7 (2.6)
Myocardial infarction	8 (3.1)	1 (0.4)
Acute myocardial infarction	3 (1.1)	2 (0.8)
Cardiac failure	3 (1.1)	0
Respiratory, thoracic and mediastinal disorders	17 (6.5)	12 (4.5)
Respiratory failure	4 (1.5)	4 (1.5)
Acute respiratory failure	3 (1.1)	1 (0.4)
Pulmonary embolism	2 (0.8)	7 (2.6)
Renal and urinary disorders	6 (2.3)	1 (0.4)
Acute kidney injury	3 (1.1)	0
Psychiatric disorders	2 (0.8)	3 (1.1)
Delirium	2 (0.8)	3 (1.1)

TESAE: treatment-emergency serious adverse event

7.6 Deaths

Deaths were analyzed by overall mortality (patients who died before the Day 30 visit) and also as TEAEs leading to death. All deaths were adjudicated.

7.6.1 Adjudication

The independent EAC adjudicated all deaths. As stated in the EAC Charter, CV deaths included deaths resulting from acute MI, sudden cardiac death, deaths due to heart

failure/cardiogenic shock, death due to ischemic stroke, death due to CV procedure, pericardial tamponade, abdominal aortic aneurysm ruptures, death due to intracranial bleeding and death due to other CV events. Unwitnessed deaths, deaths of unknown cause, and uncertain deaths were considered CV deaths.

Deaths due to intracranial bleeding included all deaths attributable to the direct consequences of bleeding (eg, mass effect/herniation, cerebral edema, neural injury/ischemia/infarction) or a complication of bleeding or its treatment (eg, perioperative injury, nosocomial pneumonia secondary to intubation, multi-organ failure) The default was to consider deaths in hospital as due to the presenting hemorrhage, unless there is a clear other intervening event such as a stroke or MI. Because of this, there were a number of CV deaths adjudicated as CV-related but not reported in cardiovascular System Organ Class.

7.6.2 AEs Leading to Death

AE leading to death were reported for 24.4% of patients in the andexanet group and 20.4% in the usual care group (Table 24). At the preferred term level, no marked differences were observed between the treatment groups, as there were small numbers of patients reported for each preferred term.

Table 24: Treatment-Emergent Adverse Events Leading to Death, Frequency ≥ 2 Patients in Either Treatment Group (Safety Set)

System Organ Class Preferred Term	Andexanet (N=262) n (%)	Usual Care (N=265) n (%)
Any TEAE leading to death	64 (24.4)	54 (20.4)
Nervous system disorders	24 (9.2)	26 (9.8)
Cerebral haemorrhage	6 (2.3)	9 (3.4)
Haemorrhage intracranial	5 (1.9)	4 (1.5)
Ischaemic stroke	3 (1.1)	0
Cerebral haematoma	2 (0.8)	2 (0.8)
Hydrocephalus	2 (0.8)	1 (0.4)
Neurological decompensation	1 (0.4)	2 (0.8)
Cerebral infarction	0	2 (0.8)
Haemorrhagic stroke	0	2 (0.8)
Infections and infestations	18 (6.9)	15 (5.7)
Pneumonia	7 (2.7)	6 (2.3)
Pneumonia aspiration	7 (2.7)	5 (1.9)
Sepsis	3 (1.1)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	11 (4.2)	5 (1.9)
Respiratory failure	4 (1.5)	4 (1.5)
Respiratory distress	2 (0.8)	0
Cardiac disorders	8 (3.1)	2 (0.8)
Cardiac failure	3 (1.1)	0
Injury, poisoning and procedural complications	0	2 (0.8)
Brain herniation	0	2 (0.8)

AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
Note: In accordance with the study protocol, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurred within the first 12 hours post-randomization were not regarded as an AE or SAE except when there was evidence suggesting a causal relationship between the drug and the event. Thus, death due to disease progression was not reported with an SAE or AE leading to death.

7.6.3 All-Cause Mortality Within 30 Days of Randomization

Overall mortality within 30 days of randomization was 28.2% in the andexanet group (74 patients) and 26.4% in the usual care group (70 patients). The number of overall deaths in the study is greater than the number of patients who had TEAEs leading to death because the cause of death was not reported as a TEAE for disease progression. In accordance with the 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. Progression of disease was less common in the andexanet group than in the usual care group (10 vs 16).

Of the patients who died before the Day 30 visit, the cause of death was adjudicated to be CV-related for all 74 patients who died in the andexanet group, and for all except one of the 70 patients who died in the usual care group (Table 25). Additionally, all of the in-hospital deaths in both treatment groups were adjudicated to be CV-related, except for one patient (0.4%) in the usual care group (preferred term of septic shock). Bleeding-related death within 72 hours post-randomization (not associated with a thrombotic event) occurred in 14 patients (5.3%) in the andexanet group and 19 (7.2%) in the usual care group.

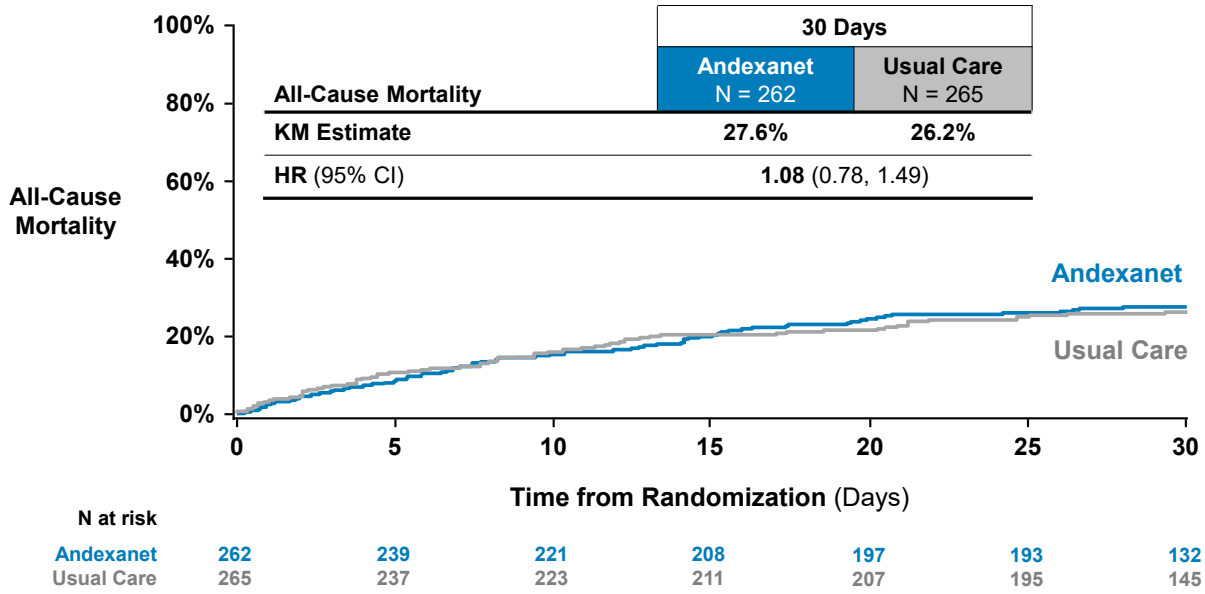
Table 25: Summary of Deaths by Cause Based on Adjudication (Safety Set)

Reason for Death, n (%)	Andexanet (N=262)	Usual Care (N=265)
All deaths	74 (28.2)	70 (26.4)
Cardiovascular*	74 (28.2)	69 (26.0)
Non-cardiovascular	0	1 (0.4)
In-hospital deaths	61 (23.3)	57 (21.5)
Cardiovascular*	61 (23.3)	56 (21.1)
Non-cardiovascular	0	1 (0.4)
Bleeding-related deaths**	14 (5.3)	19 (7.2)
Cardiovascular*	14 (5.3)	18 (6.8)
Non-cardiovascular	0	1 (0.4)

CV: cardiovascular; EAC: Endpoint Adjudication Committee; ICrH: intracranial hemorrhage.
Deaths that occurred as a consequence of ICrH are classed as CV death according to the EAC Charter;
* All intrahospital deaths following the presenting ICrH with no other apparent cause were adjudicated as CV.
**Bleeding-related death is defined as any death within 72 hours from randomization and not associated with the occurrence of an identified thrombotic event.

A similar pattern for the probability of death over time was observed between both treatment groups with the Kaplan-Meier curves crossing at several timepoints (Figure 25).

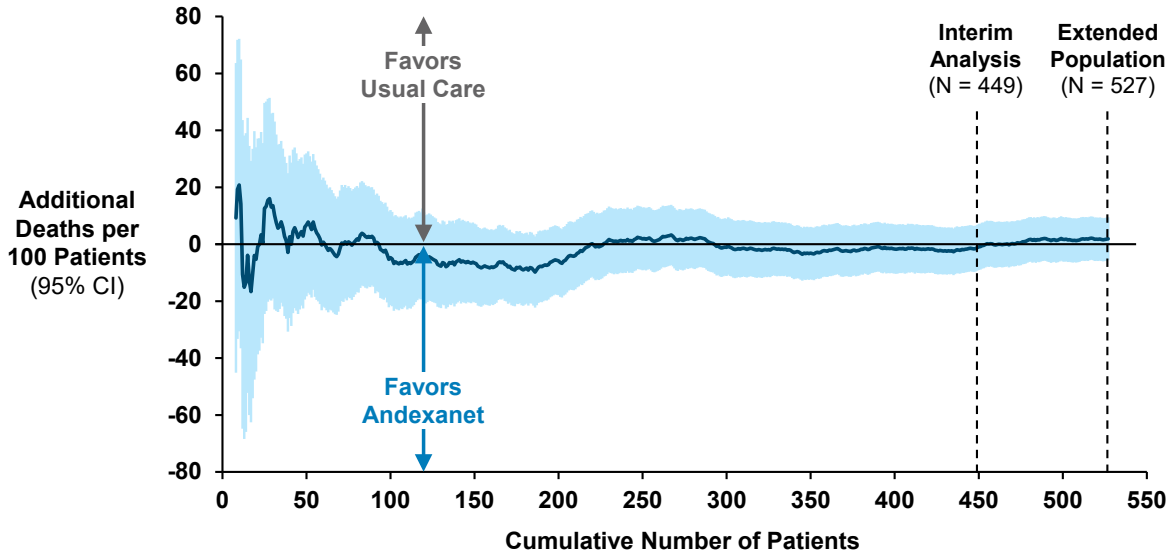
Figure 25: Kaplan-Meier Plot of All-Cause Mortality (Safety Set)



CI: confidence; HR: hazard ratio; KM: Kaplan-Meier.

The treatment difference between andexanet and usual care on 30-day mortality fluctuated during the ANNEXA-I study, from first randomized patient to data lock. Based on the patients included in the interim analysis (Primary Efficacy Population) there was a small numerical difference in favor of andexanet; however, based on the Safety Population, there was a small numerical difference in favor of usual care (Figure 26).

Figure 26: Mortality by Increasing Sample Size (Safety Set)



CI: confidence interval.
Additional events per 100 patients and 95% CIs are from Cochran-Mantel Haenszel tests stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

Exploratory subgroup analyses showed a numerical difference in mortality rates between patients who received high- and low-dose andexanet (Table 26). Further analysis of baseline characteristics revealed imbalances in patient characteristics among these non-randomized subgroups that may have contributed to the observed difference in mortality rates. Since andexanet dosing was based on the USPI, and not randomized, some differences in characteristics can be expected. Moreover, in the high dose andexanet group, there was a higher proportion of patients with a history of cardiac failure and a greater mean hematoma volume compared with the low dose andexanet group. Similar differences were not observed in corresponding patients in the usual care group. These differences are notable given that hematoma volume has been described as a strong predictor for both short- and long-term mortality in patients with intracerebral hemorrhage (LoPresti et al 2014) and heart failure has been associated with increased mortality rates (Javalkar et al 2020). In patients with cerebral hemorrhage and heart failure, 30-day mortality rates of 10%, 1-year mortality of 20% to 30%, and 5-year mortality of 45% to 60% were reported (Javalkar et al 2020). Taken together, the imbalances in baseline characteristics, including history of cardiac failure and higher hematoma volume, in ANNEXA-I likely contribute to the numerically higher incidence of death observed in the high dose andexanet group.

Table 26: Mortality Rate by Dose Eligibility and Baseline Characteristics (Safety Set)

	Andexanet		Usual Care	
Baseline Characteristic, n (%)	Low Dose N=202	High Dose N=60	Low Dose Eligible N=201	High Dose Eligible N=64
30-day mortality, n/N (%)	50 (24.8)	24 (40.0)	52 (25.9)	18 (28.1)
Hematoma volume (mL), mean	17.2	22.1	17.4	18.0
History of stroke or MI	59 (29.2)	19 (31.7)	60 (29.9)	20 (31.3)
History of cardiac failure	29 (14.4)	17 (28.3)	44 (21.9)	17 (26.6)
Hematoma volume (mL), mean	18.7	33.4	18.8	13.6

MI: myocardial infarction.
Note: Dose eligibility was determined prior to randomization for all patients.

7.7 Adverse Event of Special Interest: Thrombotic Events

7.7.1 Overview of Thrombotic Events

Anticoagulants are used to manage thrombotic conditions such as venous thromboembolism, and other conditions with a thrombotic risk such as atrial fibrillation. Given this, and the fact that bleeding itself may provoke thrombosis, occurrence of thrombotic events is not unexpected in this patient population as the reversal of anticoagulant exposes the patients to their baseline thrombotic risk.

In ANNEXA-I, the baseline median CHA_2DS_2-VASc score, which measures stroke, was 4 out of 9 in both groups.

In ANNEXA-I, the proportion of patients with a thrombotic event confirmed by adjudication through 30 days post-randomization was higher in the andexanet group than in the usual care group (Table 27). However, the observed rate in patients treated with andexanet was similar to the frequency observed in patients with adjudicated acute major bleeding in ANNEXA-4 (10.3% vs 10.5%, (Milling et al 2023)) and concordant with rates reported in clinical studies of bleeding occurring during treatment with FXa inhibitors (Chaudhary et al 2022).

Six patients (2.3%) in the andexanet group and 2 patients (0.8%) in the usual care group had an adjudicated thrombotic event leading to death (Table 28). For the andexanet group, this is 22% of the patients who experienced an adjudicated thrombotic event (6 out of 27 patients), which is similar to findings in ANNEXA-4.

Several observations can be made when looking at these andexanet-treated patient cases on an individual basis, focusing on the nature of the thrombotic event first and

then looking at the circumstances surrounding the fatality attributed to the thrombotic event.

By and large, these patients were elderly, fragile, suffered multiple comorbidities (with a high burden of thrombotic risk), and had protracted and complicated clinical stays in hospital with other important clinical conditions arising from the initial incident of intracranial bleeding. All patients but one experienced poor/none adjudicated hemostatic efficacy, which is an important prognostic indicator for mortality in these highly vulnerable patients.

All but one patient with these thrombotic events leading to death had a time to thrombotic event well outside the window of andexanet alfa activity (considering known PK/PD data) and similarly in all but one patient the Investigator had determined that the thrombotic event leading to the fatality was not related to andexanet treatment.

A single case of fatal thrombotic event emerged early on with a fatality on Study Day 2. This was a critically ill, frail patient with severe traumatic injuries who differs from other fatalities. As such the sequelae of a thrombotic event is not unexpected given their strong propensity for myocardial infarction.

Finally, it is of interest to note that of the 2 cases of fatal thrombotic event observed in the usual care group, one of the patients received no active treatment to reverse anticoagulation, highlighting the importance of potential other confounding factors involved in causing these events.

Table 27: Overview of Adjudicated Thrombotic Events (Safety Set)

Adjudication Category, n (%)	Andexanet (N=262)	Usual Care (N=265)
Any Adjudicated Thrombotic Event	27 (10.3)	15 (5.7)
Ischemic stroke	17 (6.5)	4 (1.5)
Myocardial infarction	11 (4.2)	4 (1.5)
Pulmonary embolism	1 (0.4)	6 (2.3)
Arterial systemic embolism	3 (1.1)	2 (0.8)
Deep vein thrombosis	1 (0.4)	2 (0.8)

Table 28: Adjudicated Thrombotic Events Leading to Death (Safety Set)

Preferred Term, n (%)	Andexanet (N=262)	Usual Care (N=265)
Thrombotic event leading to death	6 (2.3)	2 (0.8)
Myocardial infarction*	1 (0.4)	0
Ischemic stroke	3 (1.1)	0
Cerebral infarction	0	2 (0.8)
Cerebral ischemia	1 (0.4)	0
Peripheral ischemia	1 (0.4)	0

*Patient experienced a multi-trauma event and died on Day 2.

7.7.2 Time to Onset

The median time to onset of the first thrombotic event was 3 days in the andexanet group and 14 days in the usual care group (Table 29; see also Figure 28). During the first 3 days, 14 out of 27 patients in the andexanet group with thrombotic events had their first event, compared to 1 out of 15 patients in the usual care group. None of these patients had received any dose of anticoagulant prior to the thrombotic event, which as described in the subsequent section, is an important factor in reducing the risk of thrombotic events.

Table 29: Time of Onset of First Thrombotic Event (Safety Set)

Time to Onset, days	Andexanet (N=262)	Usual care (N=265)
Patients with thrombotic event	27	15
Mean (SD)	7.81 (8.09)	14.27 (6.58)
Median (min, max)	3.00 (1.0, 24.0)	14.00 (2.0, 24.0)
≤ 3 days	14 (5.3)	1 (0.4)
4–10 days	5 (1.9)	4 (1.5)
> 10 days	8 (3.1)	10 (3.8)

SD: standard deviation.

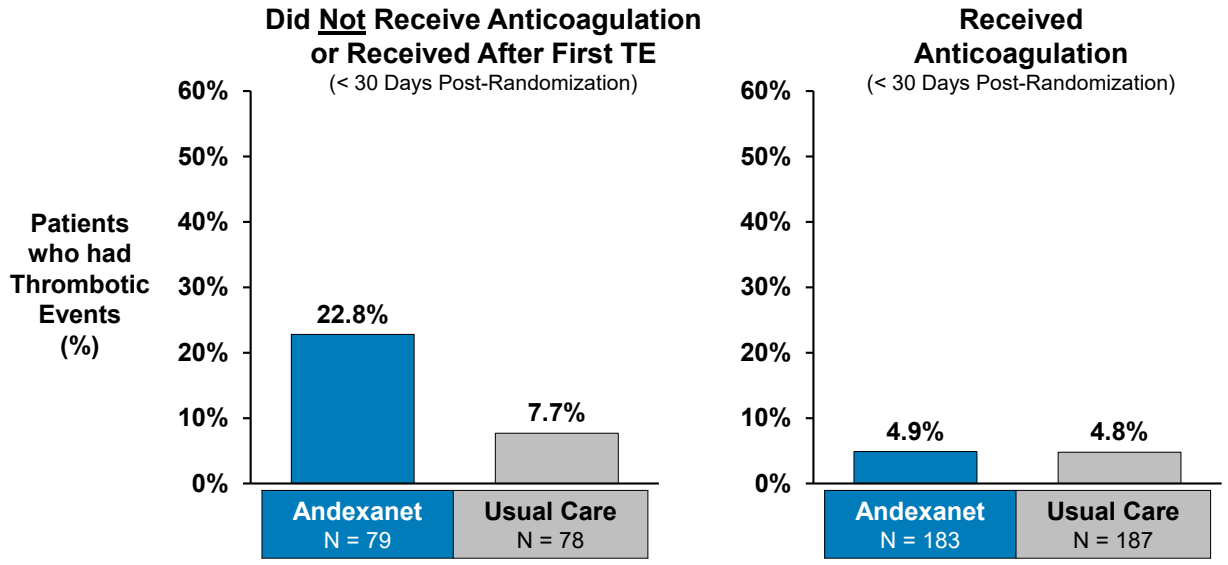
7.7.3 Restarting Anticoagulant Therapy

Analyses were performed to evaluate whether the thrombotic event rate was reduced following re-anticoagulation. Overall, 183 patients in the andexanet group and 187 patients in the usual care group received at least one dose of any anticoagulant as a prophylactic measure (Figure 27). In this population, a similar rate of thrombotic events

was observed in the andexanet and usual care group (4.9% and 4.8%, respectively), which were also consistent with the rate observed in ANNEXA-4 (4.9%).

In the patients in the andexanet group who did not receive any anticoagulation as a prophylactic measure, 18 patients (22.8%) had a thrombotic event, compared with 6 patients (7.7%) in the usual care group. These data underscore the importance of restarting anticoagulation as soon as medically appropriate, in line with the approved prescribing information.

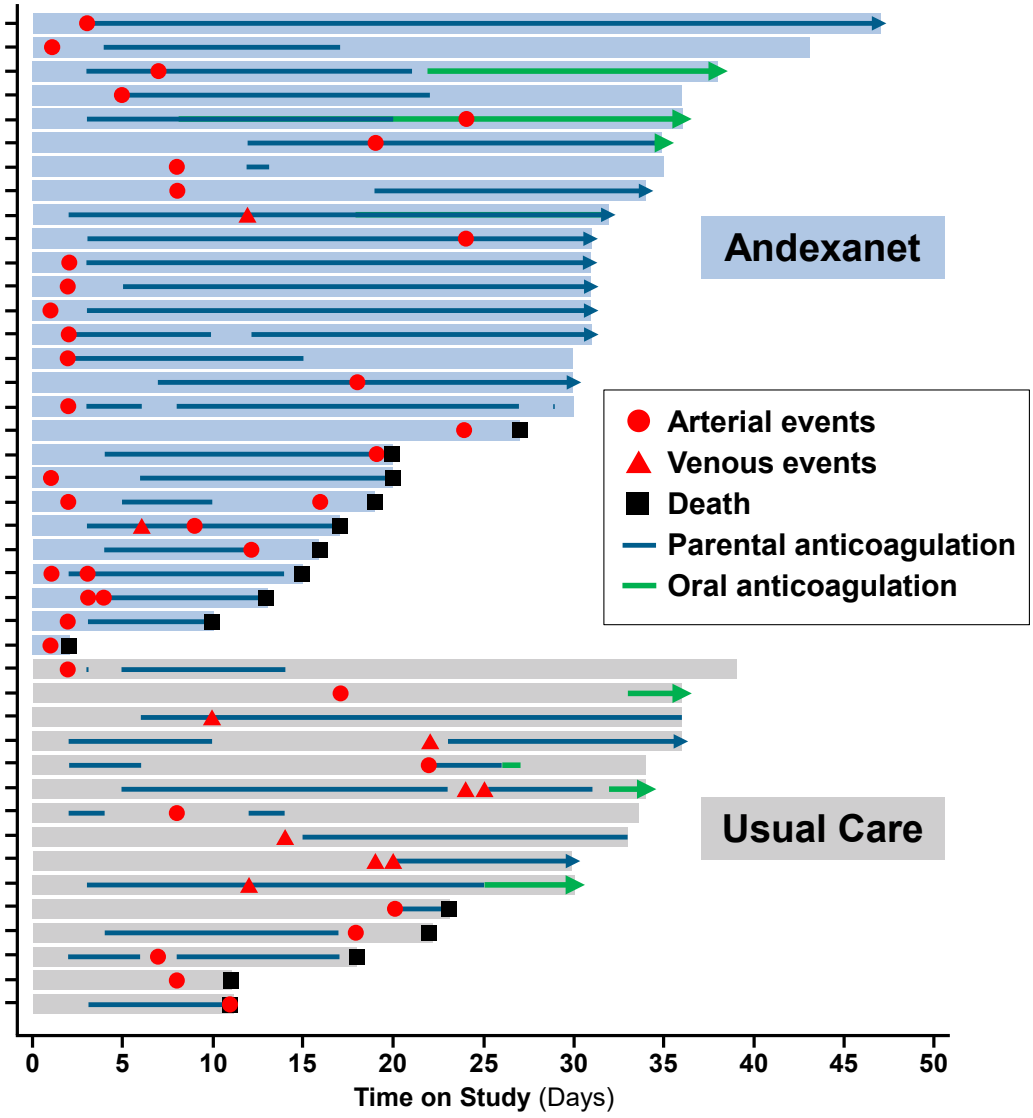
Figure 27: Thrombotic Events in Patients with/without Re-Anticoagulation in the Follow-up Period (Safety Set)



TE: thrombotic event.

The swim-lane plot displayed in Figure 28 shows the timing of and type of anticoagulant received by each patient in the context of the timing of arterial or venous thrombotic event. Treatment guidance on whether and when to start re-anticoagulation is varied, particularly depending on the location of the bleeding. The American Heart Association recommends to re-anticoagulate, using a venous thromboembolism prophylaxis dosing 24–48 hours from the index event. However, there is no guidance that definitively recommends the early restart of oral anticoagulation soon after a hemorrhage, especially regarding ICrH. Guidance often emphasizes an individualized, multidisciplinary team approach in re-anticoagulation decisions and often recommends resumption of anticoagulation weeks or months after the index event. This is illustrated by the American Heart Association guidelines where the recommendation is 7 to 8 weeks in patients with atrial fibrillation, but again only after weighing specific patient characteristics to optimize the balance of risks and benefits.

Figure 28: Re-Anticoagulation Swim Lane Plot for Patients Experiencing a Thrombotic Event (Safety Set)

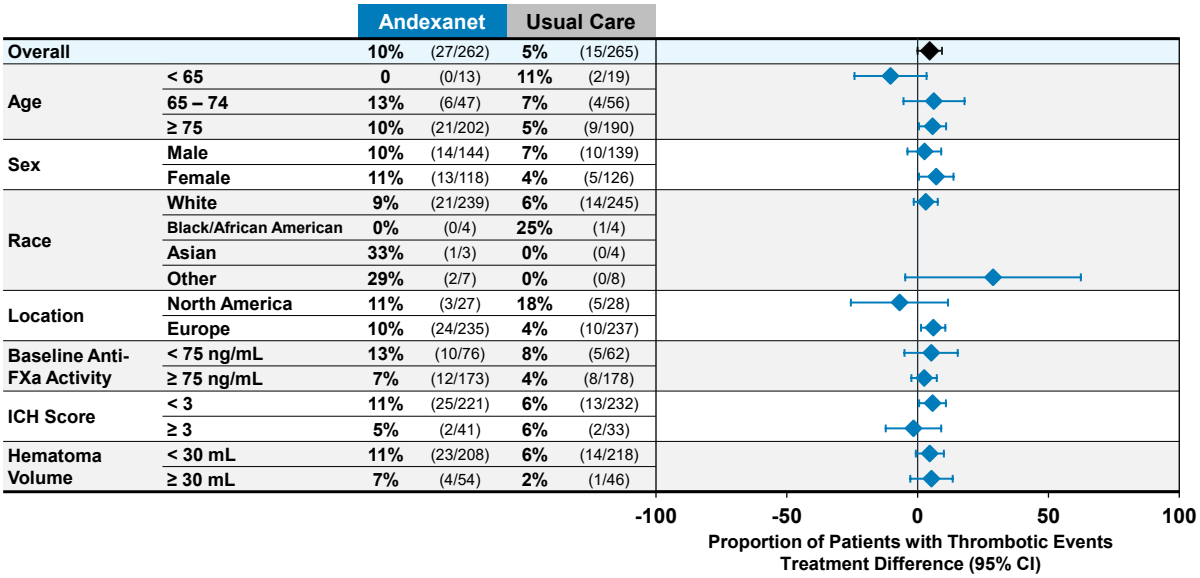


Blue shading indicates patients in the andexanet group; grey shading indicates patients in the usual care group.

7.7.4 Subgroup Analyses of Adjudicated Thrombotic Events

The difference in the rate of adjudicated thrombotic events between treatment groups across pre-defined patient subgroups was generally consistent with the overall study population (Figure 29). Numerical differences were observed in some subgroups, but the data should be interpreted with caution since the numbers of patients and events in the subgroups were small.

Figure 29: Forest Plot of Difference in Proportion of Patients with Adjudicated Thrombotic Events (Safety Set)



CI: confidence interval; FXa: activated factor X; ICH: intracerebral hemorrhage.

Post hoc analyses of adjudicated thrombotic events were also performed for a subgroup based on patients with a medical history of cardiac failure and a subgroup based on patients with a medical history of stroke or MI (Table 30). The thrombotic event rate was numerically higher in the andexanet group compared with the usual care group across both of these subgroups, in line with the results for the overall study population. However, within the andexanet group, the observed thrombotic event rates were numerically higher in the subgroup of patients with medical history of stroke or MI, and the subgroup with a medical history of cardiac failure, compared with patients who did not have a history of these underlying diseases. Importantly, these post hoc analyses based on medical histories of cardiac failure, MI or stroke did not reveal an interaction between treatment and these subgroups. The USPI has been updated to reflect these findings in the sBLA.

Table 30: Difference in Proportion of Patients with Adjudicated Thrombotic Events up to Day 30, Post Hoc Analysis Based on Medical History (Safety Set)

Medical History	Andexanet % (n/N)	Usual Care % (n/N)	Difference (95% CI)
Cardiac Failure			
Yes	17.4 (8/46)	3.3 (2/61)	14.1 (2.2, 26.0)
No	8.8 (19/216)	6.4 (13/204)	2.4 (-2.6, 7.5)
Stroke or myocardial infarction			
Yes	12.8 (10/78)	2.5 (2/80)	10.5 (2.1, 18.9)
No	9.2 (17/184)	7.0 (13/185)	2.2 (-3.4, 7.8)

CI: confidence interval.

7.8 Immunogenicity

Immunogenicity of andexanet was evaluated as a safety endpoint at baseline, at the Day 30 visit and in case of anti-andexanet antibody presence, at approximately the Day 120 visit. No antibodies (neutralizing or non-neutralizing) against FX or FXa have been identified in ANNEXA-I. The objective was also to evaluate any neutralizing potential in samples confirmed positive for anti-andexanet antibodies.

The immunogenicity results of ANNEXA-I were consistent with ANNEXA-4. Very few patients tested positive for anti-andexanet antibodies in ANNEXA-I up to Day 30 (Table 31) and titers were low, indicating a low risk of immunologic response in the andexanet group.

Table 31: ANNEXA-I Immunogenicity Results

	Andexanet		Usual Care	
	Baseline	Day 30	Baseline	Day 30
Positive for anti-andexanet antibodies, n	1[a]	2[b]	2	3[c]

a. Patient in the low dose group. No anti-andexanet antibodies detected at Day 30.
b. One patient in the low dose group and one patient in the high dose group. Both patients had no anti-andexanet antibodies detected at baseline.
c. One patient tested positive for anti-andexanet at Day 30 but not at baseline.

Given the semi-quantitative nature of the anti-andexanet antibody assay and its high sensitivity, the small number of positive anti-andexanet antibody values detected in both treatment groups likely reflects background noise as opposed to real signal in the data.

This is supported by the fact that antibodies were detected in some patients before study treatment was administered.

Currently there is no assay available for evaluating the neutralizing potential of anti-andexanet antibodies in patient samples. The commercial anti-human FX antibody lot, previously used as a positive control in this assay, has been used and is no longer commercially available. The Sponsor tried to identify a new commercial anti-human FX antibody lot suitable to act as a positive control. The performance and functionality of the antibody lots investigated do not show similar andexanet neutralizing activity and a high variability between antibody lots has been observed. This could be due to the high similarity in the structural elements between andexanet and FX. As a result, the assay activities have been put on hold while evaluating alternative options, including animal immunization and multiple rounds of B-cell cloning to potentially obtain a mix of appropriate positive monoclonal antibody binders that could interfere with the activity of andexanet and thus act as a positive control. The outcome of this work is not expected until 2025.

Based on the production method, posology, and PK, andexanet is considered to have a low risk for immunogenicity. Andexanet is produced in Chinese Hamster Ovary cells and is of human origin. The product is given as a single IV administration for an acute event (bolus dose followed immediately by a continuous infusion). In contrast to many other therapeutic proteins, andexanet has a very short elimination half-life, approximately 5 to 7 hours.

7.9 Post-Marketing Safety

From launch to 31 July 2024 the cumulative global post-marketing patient exposure to andexanet is estimated to be 64,370 patients which includes 34,551 patients in the US. No new safety signal has been identified. The post-marketing data affirms the current benefit risk assessment for andexanet.

7.10 Safety Conclusions

Safety data from ANNEXA-I supports an acceptable safety profile of andexanet in patients with acute ICrH. Most patients experienced a TEAE, and rates were similar between groups (andexanet: 85.1% vs usual care: 82.6%). In the andexanet group, the most common TEAEs were urinary tract infection, pneumonia, and hypokalemia. The safety profile was largely driven by AEs consistent with the mechanism of action of andexanet including a higher rate of thrombotic events compared to usual care (10.3% vs 5.7%). Thrombotic events are a known risk associated with andexanet as outlined in the boxed warning in the current USPI. Importantly, in patients who received an anticoagulant within 30 days after the index bleed showed a rate of thrombotic events that was similar between andexanet and usual care group (4.9% vs 4.8%), supporting language used in the approved prescribing information emphasizing the importance of restarting anticoagulation treatment as soon as medically appropriate, after andexanet

treatment. All-cause mortality through 30-days was 28.2% in the andexanet group and 26.4% in the usual care group.

The overall safety profile of andexanet in the ANNEXA-I population was consistent with the established safety profile from ANNEXA-4. There were no safety signals supporting an acceptable safety profile of andexanet in patients in the setting of uncontrolled and life-threatening bleeding events, including acute ICrH.

8 ANDEXANET REAL-WORLD DATA

ANNEXA-I is the first and largest randomized controlled study of andexanet. Therefore, it is valuable to contextualize the ANNEXA-I findings with real-world data and a recent meta-analysis. These RWE data complement the data from ANNEXA-I to help assess how andexanet can be used in real life by patients and clinicians. Individual studies have been identified through systematic literature review, and 2 key studies are summarized below. The real-world data highlighted in Section 8.1 and 8.2 are both conducted in the US and considered to have low-to moderate bias according to White et al (2024). The study by Dobesh et al, described in Section 8.1, is the largest study from the US in this patient population, including electronic health records from > 350 hospitals, and > 4,000 patients. The study by Sutton et al, described in Section 8.2, is an analysis of claims available from the US Veterans Affairs medical centers (a national integrated health system with high quality data), which allows an opportunity to follow patients during and beyond hospitalization. There are more studies conducted worldwide, and in the US, of which some are indirect comparisons to ANNEXA-4 with synthetic control arms. These are best summarized by the recent meta-analysis by White et al (2024), presented in Section 8.3.

8.1 US Multicenter Study: Andexanet vs 4F-PCC (Dobesh et al 2023)

This multicenter, observational cohort study compared andexanet to 4F-PCC across different types of acute major bleeds that occurred in patients while on apixaban or rivaroxaban. The analysis included 4,395 patients (of which 2,567 had GI bleeds and 1,328 had intracerebral hemorrhage). It was demonstrated that in-hospital mortality was significantly lower among patients treated with andexanet compared with patients treated with 4F-PCCs (6.0% vs 10.6%, adjusted OR: 0.50, $p < 0.01$) (Dobesh et al 2023). Risk reductions for in-hospital mortality were consistent for both intracerebral hemorrhage (12.6% vs 23.3%, adjusted OR: 0.55, $p < 0.01$) and GI bleeds (2.5% vs 4.3%, adjusted OR: 0.49, $p < 0.01$) (Table 32).

Table 32: In-Hospital Mortality Andexanet vs 4F-PCC

	Andexanet		4F-PCC			
	n	%	n	%	Odds Ratio (95% CI)	p-value
Overall	2122	6.0	2273	10.6	0.50 (0.39, 0.65)	< 0.01
ICrH	666	12.6	662	23.3	0.55 (0.39, 0.76)	< 0.01
GI bleed	1206	2.5	1361	4.3	0.49 (0.29, 0.81)	< 0.01

4F-PCC: Four-factor prothrombin complex concentrate; CI: confidence interval; GI: gastrointestinal; ICrH: intracranial hemorrhage; OR: odds ratio.
Source: (Dobesh et al 2023)

8.2 Cohort Study Using Data from the US Department of Veterans Affairs – Andexanet versus 4F-PCC (Sutton et al 2023)

Based on another retrospective analysis of electronic medical records and a propensity score matched analysis including 255 US patients with a major bleed associated with an FXa inhibitor, it was reported that adjusted in-hospital mortality was significantly lower when andexanet was administered (10.6%, n=85) compared to when 4F-PCC was administered (25.3%, n=170) (adjusted hazard ratio [HR] 0.31, 95% CI [0.14, 0.71], p=0.01) (Sutton et al 2023). Unlike the data set in 8.1, this much smaller dataset allowed for analysis of 30-day mortality, and similar results were observed: 20.0% in patients treated with andexanet and 32.4% in patients treated with 4F-PCC (adjusted HR 0.54, 95% CI [0.30, 0.98], p=0.039).

8.3 Meta-Analysis Andexanet vs PCC (White et al 2024)

White et al (2024) performed a recent meta-analysis to provide a pooled estimate for the effect of andexanet versus PCC products on hemostatic efficacy, in-hospital mortality, 30-day mortality, and thrombotic events. In this meta-analysis a bias assessment was performed of all studies. Low–moderate risk of bias studies were analyzed separately, as well as combined with high risk of bias studies (White et al 2024).

Studies with low–moderate risk of bias suggested improvements in hemostatic efficacy (OR: 2.72 [95% CI: 1.15–6.44]), lower in-hospital mortality (OR: 0.48 [95% CI: 0.38–0.61]), and reduced 30-day mortality (OR: 0.49 [95% CI: 0.30–0.80]) when andexanet was used versus PCC products.

8.4 Conclusions

Considering the totality of RWE, there is a consistent signal that andexanet reduces hematoma expansion and increases thrombotic events in patients with FXa inhibitor-related major bleeds compared with usual care therapies. In addition, mortality benefits have been observed both in hospital and at 30 days while a mortality benefit for andexanet is not observed in ANNEXA-I. The patients in the RWE studies were treated earlier as they did not have to be randomized (approximately 1.5 hours between scan and treatment for study procedures [Table 14]). In addition, a larger proportion of ICrH patients in the real-world studies had traumatic etiology.

9 BENEFIT-RISK CONCLUSIONS

The use of FXa inhibitors has become a standard of care in anticoagulation therapy, significantly reducing thrombotic risk for patients with conditions like venous thromboembolism and atrial fibrillation. However, this has led to an increase in FXa inhibitor-related hospital admissions due to uncontrolled, life-threatening bleeding events. In these critical situations, where every second counts, rapid and effective interventions are essential to manage the patients' immediate risk of death.

Andexanet was specifically developed to rapidly reverse the effects of FXa inhibitors, addressing a critical medical need for physicians who rely on fast-acting, targeted therapies to stop life-threatening bleeding events. Clinical evidence shows that andexanet quickly and effectively reverses FXa inhibition by more than 92% within 2 minutes following bolus administration, in patients with uncontrolled or life-threatening bleeding. This rapid onset of anti-FXa activity resulted in statistically significant and clinically meaningful hemostatic efficacy when compared to usual care in ANNEXA-I (Treatment difference [95% CI]: -13.4% [4.6, 22.2], p=0.0032).

However, andexanet is just one component of the bundle of care emergency physicians employ to save lives. In acute settings, managing FXa inhibitor-related bleeding requires a multi-faceted approach, integrating treatments like blood pressure control, surgical intervention and reversal of anticoagulant effects. Andexanet offers a specific and essential tool for reversing FXa inhibitors that is delivered alongside other interventions designed to stop the bleed and support patient survival.

Andexanet is associated with an increased risk of thrombotic events as outlined in a boxed warning in the current USPI. In ANNEXA-I, 10.3% of andexanet-treated patients compared to 5.7% of patients randomized to usual care had a thrombotic event confirmed by adjudication through 30 days post-randomization.

By rapidly reversing FXa inhibition, andexanet re-exposes patients to their underlying thrombotic risk, the very reason they were prescribed the FXa inhibitor. These risks are further heightened by the bleeding event itself, complications of the bleeding and subsequent hospitalization. The impact of the underlying thrombotic risk is illustrated by the numerical increase of thrombotic events in patients with a history of MI, stroke and cardiac failure in ANNEXA-I and as such an update to the USPI will be proposed to inform physicians. Emergency and critical care teams are fully equipped to manage these complications, ensuring that appropriate measures enforcing rapid detection, assessment and treatment are in place should a thrombotic event occur.

In emergency settings, patients on FXa inhibitors with life-threatening, uncontrolled bleeding require immediate intervention to stop the bleed, and physicians must utilize a rapid bundle of care to save the patient's life.

Once the bleed has been controlled, the medical team's focus shifts to reduce the risk of complications. A key aspect is reinitiation of anticoagulation therapy when the patient is stable, in-line with guideline recommendations, and as part of a holistic approach to the patient. Initiation of anticoagulation as soon as medically appropriate is recommended in the USPI. Data from ANNEXA-I demonstrate a similar thrombotic event rate in both treatment groups in the subset of patients who received at least one dose of anticoagulation within 30 days (4.9% vs 4.8% in patients randomized to receive andexanet and usual care, respectively). A similar finding was observed in ANNEXA-4 where the thrombotic event rate in patients that received at least one dose of re-anticoagulation was 4.9%.

In summary, andexanet is a vital tool used by emergency physicians to rapidly reverse FXa inhibitors and manage uncontrolled, life-threatening bleeding events. While thrombotic events are a known risk, they are manageable within the comprehensive acute care setting, where critical care teams are fully equipped to address these complications, with re-initiation of anticoagulation therapy being recommended once the patient is stabilized to prevent future events.

In the setting of an uncontrolled, life-threatening bleeding event caused by FXa inhibitors, the benefits and risks of andexanet should be assessed and weighed against the urgency of the intervention and imminent risk of mortality. When a life is at risk, rapid hemostasis is paramount. ANNEXA-I confirmed the findings from ANNEXA-4, demonstrating that andexanet provides the only targeted approach that effectively and rapidly reverses the anticoagulation effects of FXa inhibitors compared to usual care, addressing a critical medical need. Therefore, in the acute setting of uncontrolled, life-threatening bleeding, ANNEXA-I supports a positive benefit-risk and conversion to full approval of the currently approved indication and posology of andexanet.

10 REFERENCES

Al-Shahi Salman R, Frantzias J, Lee RJ, Lyden PD, Battey TWK, Ayres AM, et al. Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol. 2018;17(10):885-94. http://dx.doi.org/10.1016/s1474-4422(18)30253-9

Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-98S. http://dx.doi.org/10.1378/chest.08-0670

Apostolaki-Hansson T, Ullberg T, Pihlsgård M, Norrving B, Petersson J. Prognosis of Intracerebral Hemorrhage Related to Antithrombotic Use: An Observational Study From the Swedish Stroke Register (Riksstroke). Stroke. 2021;52(3):966-74. http://dx.doi.org/10.1161/strokeaha.120.030930

AstraZeneca. ANDEXXA Full Prescribing Information [Prescribing Information]. 03/2024 2024. Available from: https://medicalinformation.astrazeneca-us.com/home/prescribing-information/andexxa.html. Accessed 18 October 2024.

Balami JS, Buchan AM. Complications of intracerebral haemorrhage. Lancet Neurol. 2012;11(1):101-18. http://dx.doi.org/10.1016/S1474-4422(11)70264-2

Baugh CW, Levine M, Cornutt D, Wilson JW, Kwun R, Mahan CE, et al. Anticoagulant Reversal Strategies in the Emergency Department Setting: Recommendations of a Multidisciplinary Expert Panel. Ann Emerg Med. 2020;76(4):470-85. http://dx.doi.org/10.1016/j.annemergmed.2019.09.001

Boehringer Ingelheim International GmbH. PRAXBIND® (idarucizumab) [Prescribing Information]. 2015. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf. Accessed 18 October 2024.

Botticelli Investigators WC, Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost. 2008;6(8):1313-8. http://dx.doi.org/10.1111/j.1538-7836.2008.03054.x

Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. 1993;24(7):987-93. http://dx.doi.org/10.1161/01.str.24.7.987

Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. Stroke. 1997;28(1):1-5. http://dx.doi.org/10.1161/01.str.28.1.1

Burness CB, Perry CM. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous

thromboembolism. Drugs. 2014;74(2):243-62. http://dx.doi.org/10.1007/s40265-013-0174-4

Centers for Medicare and Medicaid Services. Medicare Part D Spending by Drug. 2022 [Available from: https://data.cms.gov/summary-statistics-on-use-and-payments/medicare-medicaid-spending-by-drug/medicare-part-d-spending-by-drug/data.]

Chaudhary R, Singh A, Chaudhary R, Bashline M, Houghton DE, Rabinstein A, et al. Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(11):e2240145. http://dx.doi.org/10.1001/jamanetworkopen.2022.40145

Christensen H, Cordonnier C, Korv J, Lal A, Ovesen C, Purrucker JC, et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. Eur Stroke J. 2019;4(4):294-306. http://dx.doi.org/10.1177/2396987319849763

Coleman CI, Dobesh PP, Danese S, Ulloa J, Lovelace B. Real-world management of oral factor Xa inhibitor-related bleeds with reversal or replacement agents including andexanet alfa and four-factor prothrombin complex concentrate: a multicenter study. Future Cardiol. 2021;17(1):127-35. http://dx.doi.org/10.2217/fca-2020-0073

Connolly SJ, Crowther M, Eikelboom JW, Gibson CM, Curnutte JT, Lawrence JH, et al. Full Study Report of Andexanet Alfa for Bleeding Associated with Factor Xa Inhibitors. N Engl J Med. 2019;380(14):1326-35. http://dx.doi.org/10.1056/NEJMoa1814051

Connolly SJ, Sharma M, Cohen AT, Demchuk AM, Czlonkowska A, Lindgren AG, et al. Andexanet for Factor Xa Inhibitor-Associated Acute Intracerebral Hemorrhage. N Engl J Med. 2024;390(19):1745-55. http://dx.doi.org/10.1056/NEJMoa2313040

Crawley RM, Anderson RL. Prevention and Treatment of Bleeding with Direct Oral Anticoagulants. Drugs. 2020;80(13):1293-308. http://dx.doi.org/10.1007/s40265-020-01345-5

CSL Behring GmbH. KCENTRA (Prothrombin Complex Concentrate (Human)) [Prescribing Information]. 2013. Available from: https://www.fda.gov/media/85512/download?attachment. Accessed 18 October 2024.

Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006;66(8):1175-81. http://dx.doi.org/10.1212/01.wnl.0000208408.98482.99

Delcourt C, Huang Y, Arima H, Chalmers J, Davis SM, Heeley EL, et al. Hematoma growth and outcomes in intracerebral hemorrhage: the INTERACT1 study. Neurology. 2012;79(4):314-9. http://dx.doi.org/10.1212/WNL.0b013e318260cbba

Dobesh PP, Fermann GJ, Christoph MJ, Koch B, Lesen E, Chen H, et al. Lower mortality with andexanet alfa vs 4-factor prothrombin complex concentrate for factor Xa

inhibitor-related major bleeding in a U.S. hospital-based observational study. Res Pract Thromb Haemost. 2023;7(6):102192. http://dx.doi.org/10.1016/j.rpth.2023.102192

Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE, et al. Defining hematoma expansion in intracerebral hemorrhage: relationship with patient outcomes. Neurology. 2011;76(14):1238-44. http://dx.doi.org/10.1212/WNL.0b013e3182143317

FAMHP. Marevan (warfarin): recall and recommendations to prescribers, pharmacists and patients. 2020 [updated 24 November 2020]. Available from: https://www.famhp.be/en/news/marevan_warfarin_recall_and_recommendations_to_prescribers_pharmacists_and_patients.]

Ghadimi K, Levy JH, Welsby IJ. Perioperative management of the bleeding patient. Br J Anaesth. 2016;117(suppl 3):iii18-iii30. http://dx.doi.org/10.1093/bja/aew358

Giugliano RP, Ruff CT, Rost NS, Silverman S, Wiviott SD, Lowe C, et al. Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke. 2014;45(8):2372-8. http://dx.doi.org/10.1161/STROKEAHA.114.006025

Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2022;53(7):e282-e361. http://dx.doi.org/10.1161/STR.0000000000000407

Hankey GJ, Patel MR, Stevens SR, Becker RC, Breithardt G, Carolei A, et al. Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012;11(4):315-22. http://dx.doi.org/10.1016/S1474-4422(12)70042-X

Hankey GJ, Stevens SR, Piccini JP, Lokhnygina Y, Mahaffey KW, Halperin JL, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. Stroke. 2014;45(5):1304-12. http://dx.doi.org/10.1161/strokeaha.113.004506

Held C, Hylek EM, Alexander JH, Hanna M, Lopes RD, Wojdyla DM, et al. Clinical outcomes and management associated with major bleeding in patients with atrial fibrillation treated with apixaban or warfarin: insights from the ARISTOTLE trial. Eur Heart J. 2015;36(20):1264-72. http://dx.doi.org/10.1093/eurheartj/ehu463

January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and

the Heart Rhythm Society. J Am Coll Cardiol. 2019;74(1):104-32. http://dx.doi.org/10.1016/j.jacc.2019.01.011

Javalkar V, Kuybu O, Davis D, Kelley RE. Factors Associated with Inpatient Mortality after Intracerebral Hemorrhage: Updated Information from the United States Nationwide Inpatient Sample. J Stroke Cerebrovasc Dis. 2020;29(3):104583. http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2019.104583

Kuohn LR, Witsch J, Steiner T, Sheth KN, Kamel H, Navi BB, et al. Early Deterioration, Hematoma Expansion, and Outcomes in Deep Versus Lobar Intracerebral Hemorrhage: The FAST Trial. Stroke. 2022;53(8):2441-8. http://dx.doi.org/10.1161/STROKEAHA.121.037974

Li L, Murthy SB. Cardiovascular Events After Intracerebral Hemorrhage. Stroke. 2022;53(7):2131-41. http://dx.doi.org/10.1161/STROKEAHA.122.036884

Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: Past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost. 2017;117(7):1230-9. http://dx.doi.org/10.1160/TH16-11-0876

LoPresti MA, Bruce SS, Camacho E, Kunchala S, Dubois BG, Bruce E, et al. Hematoma volume as the major determinant of outcomes after intracerebral hemorrhage. J Neurol Sci. 2014;345(1-2):3-7. http://dx.doi.org/10.1016/j.jns.2014.06.057

McGurgan IJ, Ziai WC, Werring DJ, Al-Shahi Salman R, Parry-Jones AR. Acute intracerebral haemorrhage: diagnosis and management. Pract Neurol. 2020;21(2):128-36. http://dx.doi.org/10.1136/practneurol-2020-002763

Menichelli D, Gazzaniga G, Del Sole F, Pani A, Pignatelli P, Pastori D. Acute upper and lower gastrointestinal bleeding management in older people taking or not taking anticoagulants: a literature review. Front Med (Lausanne). 2024;11:1399429. http://dx.doi.org/10.3389/fmed.2024.1399429

Milling TJ, Jr., Clark CL, Feronti C, Song SS, Torbati SS, Fermann GJ, et al. Management of Factor Xa inhibitor-associated life-threatening major hemorrhage: A retrospective multi-center analysis. Am J Emerg Med. 2018;36(3):396-402. http://dx.doi.org/10.1016/j.ajem.2017.08.042

Milling TJ, Jr., Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, et al. Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. Circulation. 2023;147(13):1026-38. http://dx.doi.org/10.1161/CIRCULATIONAHA.121.057844

Moore EE, Moore HB, Kornblith LZ, Neal MD, Hoffman M, Mutch NJ, et al. Trauma-induced coagulopathy. Nat Rev Dis Primers. 2021;7(1):30. http://dx.doi.org/10.1038/s41572-021-00264-3

Morotti A, Boulouis G, Dowlatshahi D, Li Q, Shamy M, Al-Shahi Salman R, et al. Intracerebral haemorrhage expansion: definitions, predictors, and prevention. Lancet Neurol. 2023;22(2):159-71. http://dx.doi.org/10.1016/S1474-4422(22)00338-6

Murthy SB, Diaz I, Wu X, Merkler AE, Iadecola C, Safford MM, et al. Risk of Arterial Ischemic Events After Intracerebral Hemorrhage. Stroke. 2020;51(1):137-42. http://dx.doi.org/10.1161/STROKEAHA.119.026207

Murthy SB, Zhang C, Diaz I, Levitan EB, Koton S, Bartz TM, et al. Association Between Intracerebral Hemorrhage and Subsequent Arterial Ischemic Events in Participants From 4 Population-Based Cohort Studies. JAMA Neurol. 2021;78(7):809-16. http://dx.doi.org/10.1001/jamaneurol.2021.0925

Octapharma. Balfaxar prescribing information [Prescribing Information]. July 2023 2023. Available from: https://balfaxar.com/wp-content/uploads/2023/07/Balfaxar_Prescribing_Information_072623.pdf. Accessed 18 October 2024.

Pannach S, Goetze J, Marten S, Schreier T, Tittl L, Beyer-Westendorf J. Management and outcome of gastrointestinal bleeding in patients taking oral anticoagulants or antiplatelet drugs. J Gastroenterol. 2017;52(12):1211-20. http://dx.doi.org/10.1007/s00535-017-1320-7

Parry-Jones AR, Järhult SJ, Kreitzer N, Morotti A, Toni D, Seiffge D, et al. Acute care bundles should be used for patients with intracerebral haemorrhage: An expert consensus statement. Eur Stroke J. 2024;9(2):295-302. http://dx.doi.org/10.1177/23969873231220235

Purrucker JC, Haas K, Rizos T, Khan S, Wolf M, Hennerici MG, et al. Early Clinical and Radiological Course, Management, and Outcome of Intracerebral Hemorrhage Related to New Oral Anticoagulants. JAMA Neurol. 2016;73(2):169-77. http://dx.doi.org/10.1001/jamaneurol.2015.3682

Sarode R, Milling TJ, Jr., Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013;128(11):1234-43. http://dx.doi.org/10.1161/CIRCULATIONAHA.113.002283

Sheth KN, Solomon N, Alhanti B, Messe SR, Xian Y, Bhatt DL, et al. Time to Anticoagulation Reversal and Outcomes After Intracerebral Hemorrhage. JAMA Neurol. 2024;81(4):363-72. http://dx.doi.org/10.1001/jamaneurol.2024.0221

Singer AJ, Quinn A, Dasgupta N, Thode HC, Jr. Management and Outcomes of Bleeding Events in Patients in the Emergency Department Taking Warfarin or a Non-Vitamin K Antagonist Oral Anticoagulant. J Emerg Med. 2017;52(1):1-7.e1. http://dx.doi.org/10.1016/j.jemermed.2016.09.028

Steiner T, Weitz JI, Veltkamp R. Anticoagulant-Associated Intracranial Hemorrhage in the Era of Reversal Agents. Stroke. 2017;48(5):1432-7. http://dx.doi.org/10.1161/STROKEAHA.116.013343

Suryanarayan D, Schulman S. Potential antidotes for reversal of old and new oral anticoagulants. Thromb Res. 2014;133 Suppl 2:S158-66. http://dx.doi.org/10.1016/S0049-3848(14)50026-6

Sutton SS, Magagnoli J, Cummings TH, Dettling T, Lovelace B, Christoph MJ, et al. Real-world clinical outcomes among US Veterans with oral factor xa inhibitor-related major bleeding treated with andexanet alfa or 4-factor prothrombin complex concentrate. J Thromb Thrombolysis. 2023;56(1):137-46. http://dx.doi.org/10.1007/s11239-023-02820-y

Tomaselli GF, Mahaffey KW, Cuker A, Dobesh PP, Doherty JU, Eikelboom JW, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020;76(5):594-622. http://dx.doi.org/10.1016/j.jacc.2020.04.053

Truven Health Analytics. DOAC Market Data Report. 2019. Data on file.

White CM, Caroti KS, Bessada Y, Hernandez AV, Baker WL, Dobesh PP, et al. Andexanet alfa versus PCC products for factor Xa inhibitor bleeding: A systematic review with meta-analysis. Pharmacotherapy. 2024;44(5):394-408. http://dx.doi.org/10.1002/phar.2925

Williams JM, Lovelace B, Christoph MJ, Li S, Guo H, Hoover M, et al. Clinical and health care resource use burden of hospitalizations for oral factor Xa inhibitor-associated major bleeding: A real-world analysis of Medicare beneficiaries. J Am Coll Emerg Physicians Open. 2023;4(3):e12956. http://dx.doi.org/10.1002/emp2.12956

Xian Y, Zhang S, Inohara T, Grau-Sepulveda M, Matsouaka RA, Peterson ED, et al. Clinical Characteristics and Outcomes Associated With Oral Anticoagulant Use Among Patients Hospitalized With Intracerebral Hemorrhage. JAMA Netw Open. 2021;4(2):e2037438. http://dx.doi.org/10.1001/jamanetworkopen.2020.37438

Yakhkind A, Yu W, Li Q, Goldstein JN, Mayer SA. Code-ICH: A New Paradigm for Emergency Intervention. Curr Neurol Neurosci Rep. 2024;24(9):365-71. http://dx.doi.org/10.1007/s11910-024-01364-9

Zhou Z, Yu J, Carcel C, Delcourt C, Shan J, Lindley RI, et al. Resuming anticoagulants after anticoagulation-associated intracranial haemorrhage: systematic review and meta-analysis. BMJ Open. 2018;8(5):e019672. http://dx.doi.org/10.1136/bmjopen-2017-019672