TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number 1.1

Protocol Title: A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor

Protocol Number:	18-513
Protocol Amendment Number:	3
Compound:	Andexanet Alfa
IND:	015089
NCT Number:	03661528
EudraCR Number:	2018-002620-17
Short Title:	Andexanet Versus Usual Care to Reverse Oral Factor Xa Inhibitor in Acute Intracranial Hemorrhage
Acronym:	Annexa-I
Sponsor Name:	Alexion Pharmaceuticals, Inc.
Legal Registered Address:	121 Seaport Boulevard, Boston, MA 02210 USA
Author:	[redacted]
Version Date:	17 Apr 2023

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VERSION HISTORY

This statistical analysis plan (SAP) for Study 18-513 is based on Protocol Version 3.0, dated 05 Dec 2022.

SAP Version	Version Date	Change	Rationale
0.2	07 Jun 2022	Not applicable	Original version
1.0	30 Nov 2022	• Updated primary efficacy analysis to using one stratification factor • Updated sensitivity analyses for the primary endpoint • Updated the analysis for secondary endpoint • Updated analyses for correlation between effective hemostasis and anti-fXa activity • Updated subgroup analysis • Updated language in the section for interim analysis for better clarification • Updated definition for the per protocol set	Changes are made to align with the Protocol Amendment V3 and to incorporate comments from regulatory agency review
1.1	17 Apr 2023	• Added clarification of two data cutoff (DCO) points • Added definition of screened set	Changes are made to clarify the data used for the interim analysis, and the final analysis; and to differentiate the screened participants from the enrolled participants.

APPROVAL SIGNATURES

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20-Apr-2023 | 11:02 EDT

[redacted], Alexion **Date dd Mmm yyyy**

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20-Apr-2023 | 10:53 EDT

[redacted], Alexion **Date dd Mmm yyyy**

[redacted]

21-apr-2023 | 12:43 IST

[redacted], AstraZeneca **Date dd Mmm yyyy**

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20-Apr-2023 | 11:13 EDT

[redacted], Alexion **Date dd Mmm yyyy**

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods and outputs for analyzing data for Protocol 18-513, titled "A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor." Standard data presentation instructions and table, figure, and listing specifications are contained in the Data Presentation Plan in a separate document.

All events and analyses occurring by Day 30 will be described in a primary clinical study report. Additional events and analyses for the period between Day 30 and Day 120 (if applicable) will be described in a safety follow-up clinical study report. All analyses and outputs described in this document are for the primary clinical study report.

1.1. Objectives and Endpoints

The overall objective of the study is to gain direct insights regarding the efficacy and safety of andexanet in Factor Xa (FXa)-anticoagulated participants with acute intracranial hemorrhage (ICrH).

The objectives, endpoints, and analysis population for each endpoint are summarized in Table 1. Attributes of the estimates for the primary efficacy analyses are found in Section 5.3.1 .

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary Efficacy	
● Evaluate the effect of andexanet versus usual care on the rate of effective hemostasis	● Effective (good and excellent) hemostasis 12 hours post-randomization as determined by the blinded EAC
Secondary Efficacy	
● Evaluate the effect of andexanet versus usual care on anti-fXa activity	● Percent change from baseline to nadir in anti-fXa activity during the first 2 hours post-randomization
Additional Efficacy	
● Evaluate the effect of andexanet versus usual care on thrombin generation	● Change from baseline in thrombin generation parameters (with ETP as the primary measure), obtained at 1 and 12 hours post-randomization
● Evaluate the effect of andexanet versus usual care on neurologic function	● Proportion of neurologic deterioration, as defined by an NIHSS score increase ≥ 4 or a GCS score decrease ≥ 2 at 24 hours post-randomization versus baseline.
	● Change from baseline in the mRS score at 30 days post-randomization.
	● Change from baseline in the NIHSS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization

Table 1: Objectives and Endpoints

Objectives		Endpoints	
		●	Change from baseline in the GCS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization
		●	Proportion of participants with a ≥ 7-point increase from baseline in the NIHSS score at 12 hours post-randomization
		●	Hemostatic efficacy evaluated using only imaging parameters
		●	Proportion of participants using rescue therapy and/or procedures between 3 and 12 hours post-randomization
●	Assess the relationship between anti-fXa activity and the achievement of effective hemostasis	●	Correlation analysis between anti-fXa activity and the achievement of effective hemostasis
●	Evaluate the effect of andexanet versus usual care on health-related quality of life	●	Health-related quality of life as assessed by the EQ-5D questionnaire at 30 days post-randomization
		●	UW-mRS score at 30 days post-randomization
Safety			
●	Evaluate the occurrence of TEs at 30 days post-randomization	●	Occurrence of TEs, confirmed by adjudication, through 30 days post-randomization
●	Evaluate in-hospital and 30-day mortality (all cause, CV, and bleeding)	●	In-hospital mortality (during index hospitalization; all-cause, CV, and bleeding)
		●	Thirty-day all-cause-, CV-, and bleeding-related mortality (defined as any death within 72 hours from randomization and not associated to the occurrence of an identified TE)
●	Evaluate the occurrence of invasive intracranial procedures post-randomization	●	Proportion of participants with invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications
●	Evaluate the length of the initial hospitalization for a primary bleeding event	●	Length of the initial hospitalization for a primary bleeding event
		●	Total time admitted to the intensive care unit during the initial hospitalization
●	Evaluate the rate of rehospitalization at 30 days post-randomization	●	Proportion of rehospitalizations, including the total number of rehospitalizations and the total number of days rehospitalized, at 30 days post-randomization
●	Evaluate AEs and vital signs	●	AEs and vital signs
●		●	Antibodies to FX, FXa, and andexanet

Table 1: Objectives and Endpoints

Objectives	Endpoints
Evaluate the immunogenicity of andexanet	• Neutralizing antibodies to FX, FXa, and andexanet

Abbreviations: AE = adverse event; CV = cardiovascular; EAC = Endpoint Adjudication Committee; EQ-5D = European Quality of Life 5-Dimension; ETP = endogenous thrombin potential; FX = Factor X; fXa = Factor Xa; GCS = Glasgow Coma Scale; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TE = thrombotic event; UW-mRS = utility-weighted modified Rankin Scale

1.2. Study Design

This is a Phase 4, randomized, multicenter clinical study designed to determine the efficacy and safety of andexanet compared to usual care (UC) in participants presenting with acute ICrH (including intracerebral hemorrhage) within 6 hours of symptom onset (from the baseline imaging scan) and within 15 hours of taking an oral FXa inhibitor (from randomization). It should be noted that Protocol Amendment (PA) V1 modified Inclusion Criterion No. 3 to limit enrollment to participants with intracerebral hemorrhage to increase the homogeneity of the study population and to clarify eligible hematoma blood volume; consequently, there may be some nonintracerebral participants enrolled.

A summary of the study design can be found as below:

- The study will use a prospective, randomized, open-label design.
- Participants will be randomized 1:1 to receive either andexanet or UC stratified as follows, as detailed in PA V1:
    - Intended PCC use (yes versus no).
    - Time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes).
- Randomization must occur within 15 hours following the last dose of the FXa inhibitor. For participants enrolled > 15 hours or where the last dose time of the FXa inhibitor is unknown, if a local anti-fXa activity level obtained within 2 hours after informed consent (as part of UC) and prior to randomization is > 100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban, and edoxaban), the participant may be enrolled, irrespective of the time of the last dose, and the participant will receive the high andexanet dosing regimen.
- UC will consist of any treatments (including no treatment) other than andexanet administered within 3 hours post-randomization that the Investigator and/or other treating physicians consider to be appropriate.
- For andexanet treatment, participants will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they receive and the amount and timing of the most recent dose, as indicated in Protocol Section 6.2. The andexanet dosing regimens to be examined in this study are as follows:

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

- Andexanet will be given via an IV bolus administered over approximately 15 minutes (low dose) to 30 minutes (high dose), followed immediately by a continuous infusion administered over approximately 120 minutes. There will be no crossover between treatment groups.
- The study duration for most participants will be up to 37 days. The study duration includes 3 study periods as follows:
  - Screening and Baseline Periods: < 1 day (Day 1)
  - Treatment Period: < 1 day (Day 1)
  - Follow-up Period (all adverse events [AEs], survival, and antibodies): 30 days (Day 1 to 30 study visit)

  Participants with a positive anti-andexanet antibody response at the Day 30 visit will have an additional visit approximately 120 days post-randomization or within 30 days from when the positive test is made known to the Investigator, whichever is later.
- The primary efficacy endpoint is effective hemostasis (excellent or good versus poor/none versus nonevaluable), based on assessment of neurologic status determined by National Institutes of Health Stroke Scale (NIHSS), the use of rescue therapy, and hematoma expansion evaluation at 12 hours post-randomization by an imaging scan (computed tomography [CT] or magnetic resonance imaging [MRI]). Effective hemostasis will be determined by an adjudication algorithm or will be adjudicated by a blinded Endpoint Adjudication Committee (EAC). The derivation of effective hemostasis is provided in Section 6.1. Refer to separate Adjudication Charter for further information.
- The EAC will also adjudicate all thrombotic events (TEs), which are reported as AEs and all deaths. TEs are adverse events of special interest (AESIs) for the study.
- Approximately 900 participants are planned to be enrolled in the study at approximately 250 sites in North America, Europe, and Asia.
- A formal interim analysis for efficacy will be performed when approximately 50% (450 participants) of the anticipated sample size has been adjudicated. The main purposes of the interim analysis are 1) to assess whether to stop the study early due to efficacy and 2) to evaluate safety. Interim analysis will be performed by an independent statistics group and evaluated by the Data Safety Monitoring Board (DSMB). Details regarding the interim analysis are presented in Section 5.9.

  A preplanned sample size re-estimation (SSR) will be performed by the DSMB-associated statistician to reassess the required size of the study population based on estimation of the primary endpoint at the interim analysis. If an increase is required, the total number of participants enrolled may be increased to 1200 participants (with an addition of 300 participants).

- There are 2 data cutoff (DCO) points in ANNEXA-I. The first DCO is for the planned interim analysis of the primary efficacy endpoint by the DSMB, after 50% of the anticipated patients have been adjudicated for effective hemostasis. If the DSMB recommend stopping the study based on the interim analysis results, the first DCO will be used for confirmatory analyses of efficacy endpoints (primary efficacy population, N = 450). Enrollment of patients will be continued without interruption from the first DCO until the stop decision is communicated; then recruitment will be closed which is the second DCO. The second DCO captures the data from all patients who participate in the study (extended population, N = 450 + X) and forms the basis for the safety analyses along with sensitivity analyses of the efficacy endpoints.

2. STATISTICAL HYPOTHESES

The primary objective of this study is to compare the rate of effective hemostasis between andexanet and UC group. The following hypothesis will be evaluated:

$$H_0: \pi_{UC} - \pi_{andexanet} = 0$$

$$H_A: \pi_{UC} - \pi_{andexanet} \neq 0$$

where π is the rate of effective hemostasis in each group.

Comparison will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes). The difference in the proportion of participants with effective hemostasis between andexanet and UC group, the corresponding 95% confidence intervals (CIs) for the difference, and the p-value for the comparison will be provided.

The analysis of efficacy will employ an alpha spending function by Lan and DeMets based on Pocock boundaries. The primary efficacy objective of the study will be considered met if the proportion of participants with effective hemostasis in the andexanet group is statistically significantly higher than that in the UC group at interim ($p < 0.0310$) or in the final ($p < 0.0277$) analysis.

3. SAMPLE SIZE DETERMINATION

Results (as of 30 Jun 2020) from the Phase 3b/4, single-arm, open-label Study ANNEXA-4 have shown that the rate of effective hemostasis is 79% (95% CI: 74% to 84%) based on evaluable participants with ICrH; the rate of effective hemostasis is 80% (95% CI of 75% to 84%) based on 340 efficacy-evaluable participants with all types of bleeding.

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

4. ANALYSIS SETS

The analysis sets to be included are shown in Table 2.

Table 2: Analyses Sets

Analysis Set	Description
Screened Set	All participants who signed an informed consent form.
ES	All participants who signed an informed consent form; screen failures are excluded.
ITT Set	All participants randomized to study intervention. Participants will be analyzed according to the study intervention they are randomized to. Participants who are randomized without signing the consent form throughout the study will not be included in the ITT Set.
SS	All randomized participants who received at least 1 dose of the study intervention. In the usual care arm, randomized participants who received no treatment will also be part of the SS. Participants will be analyzed according to the study intervention they actually received.
PPS	The PPS will include all participants in the ITT Set who did not have important protocol deviations that impact the primary efficacy assessment. Detailed rules on how to define the PPS are located in Section 6.1.

Abbreviations: ES=Enrolled Set; ITT=Intent-to-Treat; PPS=Per-Protocol Set; SS=Safety Set

5. STATISTICAL ANALYSIS

5.1. General Considerations

During the conduct of the study, the Sponsor and Investigators will be blinded to the aggregated efficacy and safety summaries. In addition, all unblinded analyses that are required to support the DSMB will be performed by an independent unblinded DSMB statistician. These analyses will be performed under the direction of the DSMB according to the analyses described the DSMB Charter. The results of these unblinded analyses will not be available to the Sponsor or Investigators until after database lock.

The safety interim analyses will follow the same procedures as the efficacy interim analysis (see Protocol Section 10.7), with the Sponsor remaining blinded to the results of these analyses unless the DSMB recommends stopping the study early.

Once the study is complete and the final database lock is performed, the study will be fully unblinded and the final analyses will be performed.

All efficacy and safety endpoint parameters will be summarized descriptively.

For continuous variables, the number of observations, mean, median, SD, first quartile, third quartile, interquartile range, and minimum and maximum values will be presented. For categorical variables, unless specified otherwise, counts and percentages will be based on the number of participants with nonmissing values in each treatment group and total. Inferential statistics will be presented only when specified.

5.1.1. Hypothesis Testing and Significance Level

For the interim analysis or the final analysis, a hierarchical testing procedure will be used to test the primary and secondary endpoints to control the overall family-wise type I error rate at 5%. At interim, the primary endpoint will be tested at a significance level of 0.0310; if the primary endpoint is statistically significant, the secondary endpoint will be tested at a significance level of 0.0310.

The same approach will be used in the final analysis with a significance level of 0.0277.

5.1.2. Coding Dictionaries

Medical history and AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA). All medications will be coded using the World Health Organization Drug Dictionary (WHODrug).

5.1.3. Statistical Software

Statistical analysis will be performed using Statistical Analysis Software (SAS) Version 9.4 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used for the production of graphics and for statistical methodology not available in SAS.

5.2. Study Participants

5.2.1. Disposition of Participants

The number of participants screened and the number of screen failures, along with reason for screen failure, will be tabulated. A by-participant listing of screen failures will be provided.

The number of participants randomized to each treatment (andexanet or UC) and overall (total) and the number of participants in the Safety Set, Intent-to-Treat (ITT) Set, and Per-Protocol Set (PPS), along with percentages, will be tabulated. In addition, the number of participants randomized to each treatment and total will be tabulated for the stratification factors (intended PCC use [yes versus no] and the time from symptom onset to the baseline imaging scan [< 180 minutes versus ≥ 180 minutes]).

A by-participant listing showing population set status, along with randomization information, will be provided.

Enrollment by region (North America, Europe, and Asia), country, and site will be tabulated by treatment group and total.

An accounting of study participant disposition will be tabulated and will include the number and percentage of participants who completed the study (completing the 30-day Follow-up Visit for all participants) and who discontinued study early within each treatment and total, as well as the reason for discontinuation from the study. Descriptive statistics will be provided for the study duration and will be based on all participants at the time of either the interim data cutoff or the final locked dataset, as applicable.

In addition, the number and percentage of participants who fail inclusion/exclusion criteria will be tabulated by treatment group and total and will specify the protocol version under which the failure occurred.

By-participant listings tabulating participant disposition data will be provided.

5.3. Primary Endpoint Analysis

The primary objective of the study is to compare the rate of participants with effective hemostasis 12 hours post-randomization between andexanet and UC. The primary endpoint is based on the achievement of effective hemostasis, as determined by the blinded EAC based on prespecified criteria documented in the Adjudication Charter.

Effective hemostasis will be further defined as follows:

- 1 = for participants with effective hemostasis rated as excellent/good
- 0 = for participants with effective hemostasis rated as poor/none

Refer to Section 6.1, for details on how the primary efficacy endpoint is determined, including the handling of missing data.

The primary analysis will be performed on the ITT Set.

5.3.1. Estimand

Table 3 below describes the attributes of the Primary (Composite) estimand.

Table 3: Attributes of Primary (Composite) Estimand

Estimand	Attributes of Estimand				
	Treatment	Endpoint	Population	Intercurrent Events Handling	Statistical Summary
Primary (composite estimand)	Andexanet vs usual care	Proportion of participants with effective hemostasis	ITT Set	Rescue medications/procedures: All participants will be considered as poor/none (not effective) for effective hemostasis if meeting Criteria 1 and/or 2 below: 1. Initiation of rescue therapies (medication or procedures) starting ≥ 3 hours post-randomization and up to < 12 hours post-randomization. 2. Initiation of andexanet among usual care participants, starting ≥ 3 hours after randomization and up to < 12 hours post-randomization. Missing/out-of-window/ uninterpretable/confounded events: All participants will be referred to EAC for determination of effective hemostasis if meeting Criterion below. The decision of the EAC will be considered final. 1. Insufficient information available to determine change from baseline to 12 hours in NIHSS including participants who have been intubated or sedated during these assessments. 2. Insufficient imaging information (ie, missing, out-of-window, or uninterpretable imaging scan) to determine	Difference in the proportion of participants with effective hemostasis between the 2 treatment groups, and its 95% confidence interval as estimated by a CMH test stratified by the time from symptom onset to baseline imaging assessment (< 180 minutes vs ≥ 180 minutes)

Table 3: Attributes of Primary (Composite) Estimand

Estimand	Attributes of Estimand				
	Treatment	Endpoint	Population	Intercurrent Events Handling	Statistical Summary
				change from baseline to 12 hours in hematoma volume. 3. Core imaging laboratory request for EAC review. 4. Misadministration of procoagulant blood products contrary to treatment allocation within 3 hours pos-randomization (including andexanet in usual care arm) 5. Performance of a surgery or interventional procedure to treat the index hematoma or that could impact hematoma volume within 3 hours post-randomization Nonevaluable events: There are 2 types of reasons for nonevaluable hemostatic status: 1. Cases deemed nonevaluable due to administrative reasons (for example, but not limited to, follow-up scan not available, not performed, not interpretable, or transfer of the participant to another facility for administrative purposes) 2. Cases deemed nonevaluable due to clinical reasons (for example, but not	

Table 3: Attributes of Primary (Composite) Estimand

Estimand	Attributes of Estimand				
	Treatment	Endpoint	Population	Intercurrent Events Handling	Statistical Summary
				limited to, the participant died due to index bleed or the participant had unplanned surgery draining hematoma) The decision of the EAC is considered final. The nonevaluable status due to both reasons will be treated as poor/none in the primary analysis.	

Abbreviations: CMH = Cochran-Mantel-Haenszel; EAC = Endpoint Adjudication Committee; ITT = Intent-to-Treat; NIHSS = National Institutes of Health Stroke Scale

5.3.2. Main Analytical Approach

Primary analysis will be performed using a CMH test stratified by time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes). The difference in the proportion of participants with effective hemostasis, its 95% CI, and the p-value will be estimated.

A by-participant listing of effective hemostasis will be provided.

5.3.3. Sensitivity Analysis

The following sensitivity analysis will be performed to evaluate the robustness of the primary efficacy results:

Sensitivity analysis 1: The same analysis for the primary endpoint described in Section 5.3.2 with 2 stratified factors in the CMH test: intended PCC use (yes versus no) and the time from symptom onset to baseline imaging assessment (< 180 minutes versus ≥ 180 minutes). For this analysis, participants who do not have intended PCC use data collected will be excluded.

Sensitivity analysis 2: The same analysis for the primary endpoint described in Section 5.3.2 on the PPS.

Sensitivity analysis 3: The same analysis for the primary endpoint described in Section 5.3.2 on the ITT Set, excluding participants with nonevaluable hemostatic status due to administrative reasons.

Sensitivity analysis 4: To evaluate the impact of the missing hemostatic status due to administrative reasons, 3 statistical methods for missing data imputation will be applied on the ITT Set as follows:

Worst-case scenario imputation. In this case, missing hemostatic status in the andexanet group will be imputed as poor/none, whereas missing status in the UC group will be imputed as excellent/good. The same method used in the primary analysis described in Section 5.3.1 will be used to compare andexanet and UC. This imputation represents the worst possible case for missing hemostatic status; if the statistical comparison reaches significance ($p < 0.05$), the following imputation methods will not be performed.

Jump-to-control imputation. This approach imputes missing hemostatic status using only data from the UC group. For a given participant with missing status, his/her status will be generated based on the probability of effective hemostasis in the UC group estimated with available data, regardless of the treatment group this participant is randomized to.

Tipping point. In this case, missing hemostatic status will be imputed over a series of scenarios to evaluate at what point the significance in andexanet and UC comparison will be overturned.

A logistic regression model will be first estimated for the effective hemostasis, with treatment group and time from symptom onset to the baseline imaging scan in the model. Then, a shift parameter δ will be applied to the log odds ratio in the logistic regression model to impute the missing data.

The shift parameter will take a series of values; for each value, the imputation will be applied to generate 100 datasets, and the same stratified CMH method as described in Section 5.3.1 will be used to compare andexanet and UC. Rubin's rule (Rubin, 1967) will be applied to combine results.

At the end of this process, a plot for the p-values with the shift parameter values will be generated to evaluate the impact of missing data imputation to the statistical comparison.

Sensitivity analysis 5: The primary endpoint will be analyzed by a CMH method with a 5-stratum stratification factor. The 5 strata are:

- Participants enrolled prior to Protocol Amendment V1 who were randomized not by stratifying intended PCC use (yes versus no)
- Participants enrolled after Protocol Amendment V1, and with intended PCC use and the time from symptom onset to baseline imaging assessment < 180 minutes
- Participants enrolled after Protocol Amendment V1, and with intended PCC use and the time from symptom onset to baseline imaging assessment ≥ 180 minutes
- Participants enrolled after Protocol Amendment V1, and with no intended PCC use and the time from symptom onset to baseline imaging assessment < 180 minutes
- Participants enrolled after Protocol Amendment V1, and with no intended PCC use and the time from symptom onset to baseline imaging assessment ≥ 180 minutes

5.4. Secondary Endpoint Analysis

The secondary objective of this study is to evaluate the effect of andexanet versus UC on anti-fXa activity. The secondary endpoint is the percent change in anti-fXa activity from baseline to nadir during the first 2 hours post-randomization.

Analyses for anti-fXa activity will be based on the ITT Set. Change and percent change from baseline at each scheduled time point and from baseline to nadir 2 hours post-randomization will be summarized by treatment group. Baseline is defined as the last assessment prior to randomization.

Andexanet and UC will be compared by ANCOVA on the ranked percent change from baseline to nadir 2 hours post-randomization, adjusted for covariates of time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes) and baseline anti-fXa activity. Missing data for this analysis will be handled as follows:

Section 6.1 details the handling of missing baseline data and data above and below the upper and lower limit of quantitation.

Participants with missing baseline value will be excluded from the analysis. Remaining missing data at 1 and 2 hours post-randomization will be imputed using the multiple imputation method described by Rubin (1967). Covariates included in the imputation model include treatment group, time, time-by-treatment interaction, and baseline anti-fXa activity. Based on the imputed datasets, nadir value and percent change from baseline to nadir will be derived. ANCOVA on the ranked percent change to nadir will be used to generate the p-value for comparing andexanet and UC. This imputation process will be run 100 times, and 100 p-values will be generated; the median p-value rule, as outlined in Eekhout et al (2017), will be applied to derive the final p-value.

Figures displaying the line plots of anti-fXa activity by treatment group at baseline and at 1 and 2 hours post-randomization and boxplots at baseline and nadir by treatment group will be presented overall and for each prior FXa inhibitor.

5.5. Additional Endpoint Analysis

The tertiary efficacy endpoints are listed in Section 1.1. All tertiary efficacy analyses will be performed on the ITT Set. No missing data will be imputed.

5.5.1. Thrombin Generation

Thrombin generation will be measured from plasma samples to assess the anticoagulant effect of FXa inhibitors. Tissue factor-dependent thrombin generation will be performed at a central laboratory. Five parameters related to thrombin generation are measured as follows: endogenous thrombin potential (ETP; the primary measure), peak height, time to peak height, laboratory time, and velocity index. Thrombin generation parameters will be obtained at baseline and at 1 and 12 hours post-randomization.

Descriptive statistics for change and percent change from baseline will be provided for each parameter by treatment group and by visit.

The difference between the 2 treatment groups in ETP change from baseline will be evaluated using an MMRM, adjusting baseline ETP value. The least-squares (LS) mean difference in

change from baseline and its 95% CI will be reported at 1 and 12 hours post-randomization visit, as well as across all post-randomization visits through 12 hours.

The MMRM model that analyzes ETP will contain the following fixed-effect terms:

- Time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes)
- Treatment group (andexanet versus UC)
- Visit (baseline, 1 and 12 hours post-randomization)
- Treatment-by-visit interaction

Participants will be treated as a random effect to take account of the correlation of the measurements within the same participant. An unstructured covariance matrix will be used to model within-participant variances. This model imposes no assumptions on mean trend and correlation structure and is considered robust. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation. If there is a convergence problem due to the unstructured covariance matrix, the unstructured covariance matrix will be replaced by other covariance matrices in the following order until convergence is met: autoregressive of order 1 [AR(1)], Toeplitz, and compound symmetry.

By-participant listings of thrombin generation parameters will be provided.

5.5.2. Neurologic Deterioration at 12 and 24 Hours

The proportion of participants with neurologic deterioration at 12 hours, defined as the number of participants with a ≥ 7-point increase from baseline to 12 hours in NIHSS, will be tabulated. Neurologic deterioration at 24 hours is deteriorations meeting at least 1 of the following 2 criteria.

- An increase in the NIHSS score ≥ 4 at 24 hours post-randomization compared with baseline.
- A decrease in the Glasgow Coma Scale (GCS) score ≥ 2 at 24 hours post-randomization compared with baseline.

A CMH test stratified by time from symptom onset to the baseline imaging scan will be used to compare andexanet and UC in the proportion of neurologic deterioration at 12 and at 24 hours post-randomization, respectively. The difference in the proportion and its 95% CI will be reported.

By-participant listings of neurologic deterioration at 12 and 24 hours will be provided.

5.5.3. Modified Rankin Scale

The modified Rankin Scale (mRS) score will be obtained at baseline (premorbid) and at 30 days post-randomization or at the Early Termination Visit. If the baseline mRS is unavailable during Screening, the mRS can be collected from the participant, relative, caregiver, or legally authorized representative at a post-randomization time point as long as the mRS reflects the participant's premorbid (ie, pre-ICrH) neurologic status. The premorbid mRS should reflect the

participant's neurologic status prior to acute illness. Tabulation of mRS scores at baseline and Day 30 will be provided by treatment group.

mRS at 30 days post-randomization will be dichotomized into 1 (functional independence: scores of 0, 1, 2, and 3) and 0 (functional dependence: scores of 4 and 5; death: score of 6). A logistic regression model will be used to analyze mRS at Day 30, adjusting for baseline mRS, time from symptom onset to the baseline imaging scan, and treatment group. The odds ratio for the treatment effect with 95% CI will be reported.

Summaries of shifts in functional independence from baseline to Day 30 will also be provided by treatment group.

By-participant listings of mRS will be provided.

5.5.4. NIHSS and GCS Through 72 Hours Post-randomization

Values of NIHSS and GCS at each visit and change and percent change from baseline at 2, 3, 6, 12, 24, and 72 hours post-randomization will be summarized by treatment group.

For both NIHSS and GCS, the difference between the 2 treatment groups in NIHSS and GCS change from baseline will be evaluated using MMRM separately, adjusting baseline scores. The LS mean difference in change from baseline and its 95% CI will be reported for each post-randomization visit, as well across all post-randomization time points through 72 hours.

The MMRM model that analyzes NIHSS and GCS will contain the following fixed-effect terms:

- Time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes)
- Treatment group (andexanet versus UC)
- Visit (baseline, 2, 3, 6, 12, 24, and 72 hours post-randomization)
- Treatment-by-visit interaction

Participants will be treated as a random effect to take account of the correlation of the measurements within the same participant. An unstructured covariance matrix will be used to model within-participant variances. This model imposes no assumptions on mean trend and correlation structure and is considered robust. Denominator degrees of freedom will be estimated using the Kenward-Roger approximation. If there is a convergence problem due to the unstructured covariance matrix, the unstructured covariance matrix will be replaced by other covariance matrices in the following order until convergence is met: AR(1), Toeplitz, and compound symmetry.

By-participant listings of NIHSS and GCS data will be provided.

5.5.5. Effective Hemostasis With CT or MRI Scan

Effective hemostasis using only imaging parameters will be evaluated. The imaging parameter refers to change in hematoma volume between baseline and 12 hours by CT or MRI scan. An increase ≤ 35% is considered excellent/good whereas a change > 35% is considered as poor/none. A CMH test stratified by time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes) will be used. The difference in the proportion of

participants with effective hemostasis using only imaging parameters and its 95% CI will be estimated.

By-participant listings of effective hemostasis with CT or MRI Scan will be provided.

5.5.6. Rescue Therapy

Rescue therapies include rescue medications and rescue procedures including surgeries. The number of participants receiving rescue therapies (medication or procedures) between 3 and 12 hours post-randomization, as well as the total number of therapies received, will be summarized based on dose of andexanet received (low, high, and total) or the type of UC initially received (PCC, other, no treatment, and total). The CMH test stratified by time from symptom onset to the baseline imaging scan will be used to test the treatment difference in the proportion of participants receiving at least 1 rescue therapy between andexanet and UC. The p-value and 95% CI of the difference in proportion will be presented.

The types of rescue medications used will be tabulated by treatment group; participants reporting > 1 medication within an Anatomical Therapeutic Chemical (ATC) classification or a generic name will be counted only once for that class or name. In addition, the surgeries/procedures used to treat the index hematoma or could impact hematoma volume will be tabulated by treatment group; participants reporting > 1 surgery/procedure will be counted only once for that surgery/procedure.

A by-participant listing of rescue therapies will be provided.

5.5.7. Correlation Between Anti-fXa Activity and Effective Hemostasis

The correlation between the achievement of effective hemostasis and the percent change from baseline to nadir in anti-fXa activity 2 hours post-randomization will be evaluated. Missing data of anti-fXa activity will be imputed using the multiple imputation method described in Section 5.4. Nonevaluable effective hemostasis status will be treated as poor/none regardless of reason. A logistic regression will be used for the analysis, where the dependent variable is effective hemostasis status, the independent variable is the treatment group, and covariates include time from symptom onset to the baseline imaging scan, percent change from baseline to nadir in anti-fXa activity, and baseline anti-fXa activity. From this model, the odds ratio for the treatment effect, the area under the curve (AUC) with varying threshold for percent change from baseline to nadir in anti-fXa activity, and the 95% CI will be estimated. The same analysis will also be performed for change from baseline to nadir in anti-fXa.

5.5.8. European Quality of Life 5-Dimension 5-Level

Health-related quality of life assessed by the European Quality of Life 5-Dimension (EQ-5D) questionnaire at 30 days post-randomization is collected either on the participant or through a medical proxy. For analyses, data for both participant and proxy will be pooled. The pooled data will be summarized by treatment group by European Quality of Life 5-Dimension 5-Level (EQ-5D-5L). Comparison between andexanet and UC will be performed for each dimension in terms of “no problems” (Level 1) and “any problems” (Levels 2, 3, 4, and 5), using a CMH test adjusting time from symptom onset to the baseline imaging scan.

The EQ-5D-5L index value and visual analog scale will be summarized as continuous variables. The difference between treatment groups will be evaluated using an ANCOVA adjusted for time from symptom onset to baseline imaging scan. The LS mean difference between the 2 treatment groups and its 95% CI will be presented.

By-participant listings of EQ-5D-5L data will be provided.

5.5.9. Utility-Weighted mRS

Details on calculation of utility weights are specified in Section 6.3.2. The mean and SD of the utility values will be presented for each mRS score by treatment group.

5.6. Additional Analysis

Values at each visit and change and percent change from baseline in tissue factor pathway inhibitor (TFPI) data at baseline (most recent measurement within 15 minutes prior to randomization), at 1, 2, and 12 hours, and at Day 30 post-randomization will be summarized using descriptive statistics.

By-participant listings of TFPI data will be provided.

5.7. Safety Analyses

Safety endpoints are listed in Section 1.1. Generally, all safety analyses will be based on the Safety Set. If the study is stopped after interim analysis, safety analyses will be based on the final data cutoff unless otherwise specified.

5.7.1. Extent of Exposure

Participant compliance with the assigned treatment will not be evaluated as all procedures are performed in the hospital by a trained professional.

For the participant who received andexanet, summaries will be presented by the dose of andexanet received (low, high, and total). The number and percentage of participants with any treatment modification (dose not changed, study drug interrupted, study drug withdrawn, dose reduced, dose increased, not applicable, and unknown), along with descriptive statistics on the length of bolus and infusion duration, will be summarized.

For participants who received UC, the following data will be tabulated by the type of UC initially received (PCC, other, no treatment, and total):

- Whether PCC was used to acutely manage the participant
- The initial number of therapies received
- The therapy received

By-participant listings of andexanet and UC administration will be provided.

5.7.2. Adverse Events

AEs are defined in Protocol Section 8. An AE is any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, regardless of causal attribution

to study treatment or procedure. A treatment-emergent adverse event (TEAE) is any AE that occurs at any time following treatment initiation.

The number of events and the number and percentage of participants who experienced at least 1 TEAE reported through the Day 30 Follow-up Visit will be presented. TEAEs that are considered by the Investigator to be related to either the study intervention or the UC, TEAEs that lead to early withdrawals of study drug, and serious adverse events (SAEs) will be summarized in the same manner.

All SAEs and TEAEs leading to study intervention withdrawal or interruption will be listed separately.

5.7.2.1. Overall Summary of AEs

An overall summary of AEs and SAEs will be presented. The number of AEs and the number of participants with AEs (n, %) will be shown by treatment group and total (Table 4).

Table 4: AEs and SAEs

Events
Any TEAE
Any TESAE
Any related TESAE
Deaths
TEAEs leading to withdrawal or interruption of study intervention
TESAEs leading to withdrawal or interruption of study intervention
TEAEs by relationship (related and not related)
TEAEs by severity (mild, moderate, and severe)[a]
TESAEs by relationship (related and not related)
AESIs (thrombotic events: arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, stroke, and transient ischemic attack)

[a] Severe includes life-threatening and fatal events.
Abbreviations: AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event

5.7.2.2. AEs and SAEs by SOC and PT

The number of TEAEs and the number and percentage of participants with events will be presented by System Organ Class (SOC) and Preferred Term (PT). Participants are counted once in each SOC and PT. Percentages will be based on the total number of treated participants in each treatment group and total (andexanet plus UC). SOCs will be listed in alphabetical order, and PTs within each SOC will be sorted by descending frequency of participants, reporting the TEAEs in the total column.

TESAEs, TEAEs leading to interruption and withdrawal of study drug, frequent TEAEs including PTs with an incidence rate of ≥ 5%, and adjudicated TEs leading to death will be tabulated in a similar manner.

5.7.2.3. AEs and SAEs by SOC, PT, and Relationship

The number and percentage of participants with events will be presented by SOC and PT, as described above, by the highest relationship (related or not related). If a participant has > 1 occurrence of a TEAE with different relationship status, the related occurrence will be summarized for each participant per SOC/PT. In addition, the number of TEAEs and the number and percentage of participants with TEAEs will be presented by SOC and PT for all relationship levels (related and not related); if a participant has multiple events at the same relationship status for a particular SOC or PT, he/she is counted only once for that SOC or PT, but all occurrences are counted at the event level. SAEs will be summarized similarly.

Treatment-related TEAEs will also be tabulated, at the PT level only, for the number and percentage of participants, as well as for the number of events, with PTs sorted by descending frequency of participants, reporting the PTs in the total column.

5.7.2.4. AEs and SAEs by SOC, PT, and Severity

The number and percentage of participants with events will be presented by SOC and PT, as described above, by worst severity (mild, moderate, or severe). If a participant has > 1 occurrence of a TEAE, the most severe occurrence will be summarized for each participant per SOC/PT. In addition, the number of TEAEs and the number and percentage of participants with events will be presented by SOC and PT for all severity levels. If a participant has multiple events at the same severity for a particular SOC or PT, he/she is counted only once for that SOC or PT, but all occurrences are counted at the event level.

5.7.2.5. Deaths

The number and percentage of participants with AEs leading to death will be presented by SOC and PT as described above.

All deaths will be assessed by the EAC blinded to treatment group. Deaths occurring up to 30 days post-randomization will be referred below as 30-day death or 30-day mortality. Bleeding mortality is defined as deaths occurring within 72 hours post-randomization not associated with TEs.

All 30-day deaths, 30-day death occurring during index hospitalization, and bleeding-related mortality (defined as any death within 72 hours from randomization and not associated to the occurrence of an identified TE) will be summarized by treatment group and total based on the following causes:

- All causes
- Cardiovascular (CV) causes (resulting from myocardial infarction, sudden cardiac death, heart failure, stroke, cerebral vascular procedures, CV hemorrhage, or other)
- Non-CV causes (resulting from non-CV hemorrhage and non-CV procedure or surgery)

Time to death by all causes up to 30 days post-randomization will be analyzed using a Cox proportional hazards model adjusted for time from symptom onset to the baseline imaging scan (< 180 minutes versus ≥ 180 minutes) and treatment group. Participants who did not die or discontinued prior to Day 30 will be censored at the day of the last assessment.

Kaplan-Meier method will be used to analyze time to death with the same censoring rule. Participants who completed the study (ie, Day 30) will be censored at the day of the last assessment. Probabilities of 30-day death at different time points and median time to death will be presented by treatment group.

5.7.2.6. Adverse Events of Special Interest

The AESI for this study is TEs, which are adjudicated by EAC blinded to treatment. The number and percentage of participants with adjudicated TEs and the number of TEs in each treatment group and total will be summarized by SOC and PT.

Among participants with TEs, the number and percentage of participants in each treatment group will be summarized for the following categories:

- Did not use anticoagulants
- Used anticoagulants before the first TE
- Used anticoagulants after the first TE

5.7.3. Laboratory Tests

Testing related to clinical laboratory is defined in Protocol Section 9.2.2.

The following assays will be performed at the local laboratory:

- Hematology: Hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, and WBC differential
- Coagulation: International normalized ratio
- Serum chemistry (if available per clinical routine): Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, calcium phosphorus, and total, direct, and indirect bilirubin
- Serum or urine pregnancy test (in female participants of childbearing potential)
- Anti-fXa activity (for participants treated with an oral FXa inhibitor > 15 hours prior to randomization or unknown time of the last dose)

The following assays will be performed at a central laboratory:

- Anti-fXa activity (Note: The evaluation of the secondary efficacy endpoint will use only central, and not local, anti-fXa activity)
- Antibodies to FX, FXa, and andexanet
- Neutralizing antibodies to fX, FXa and andexanet (modified Bethesda assay [BU/mL])
- Thrombin generation
- TFPI

Analyses of clinical chemistry, hematology, and coagulation parameters will be performed by treatment.

Descriptive statistics will be performed for the values at each visit, as well as change from baseline to each visit. Tabulations will be performed for abnormal values relative to normal ranges at each visit, as well as shifts from baseline to each visit.

Clinically significant laboratory test abnormalities apply to the following analytes:

- Hematology: Hemoglobin, hematocrit, WBC count, platelet count, and WBC differential
- Serum chemistry (if available per clinical routine): Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, calcium phosphorus, and total, direct, and indirect bilirubin

Section 6.1 details the clinically significant criteria to be followed.

5.7.4. Vital Signs

Vital signs, including temperature, systolic blood pressure, diastolic blood pressure, heart rate, and respiratory rate, will be summarized using actual values and change from baseline at prespecified time points for each treatment group and total. In addition, the number of participants having clinically significant vital signs at each visit will be tabulated. Section 6.1 details the clinically significant criteria to be followed.

A by-participant listing of vital sign results will be provided.

5.7.5. Hospitalizations

Hospitalization endpoints include the following:

- Length of the initial hospitalization for a primary bleeding event. The first duration (in hours) is from the initial hospitalization to randomization, and the second duration (in days) is from randomization to the first discharge date. The total duration from the initial hospitalization to the first discharge date will also be summarized.
- Total time (in days) admitted to the intensive care unit (ICU) during the initial hospitalization.
- Rate of rehospitalization, including the total number of rehospitalizations and the total number of days rehospitalized, at 30 days post-randomization.

The length of the initial (index) hospitalization, the total time spent in the ICU, and the occurrence of rehospitalizations (including the total number of rehospitalizations and the total number of days rehospitalized) up to 30 days post-randomization will be summarized descriptively by treatment group and total.

If the time between consecutive hospitalizations is < 6 hours apart and the discharge location for the first event is either an ICU or an “inpatient non-ICU” environment, then these events are considered to be a single hospitalization. If, however, the discharge location of the first event is home care, home hospice, long-term care hospital, intermediate care facility, outside hospital, or

other, then the subsequent event is to be considered a rehospitalization regardless of the time between the events.

By-participant listings of the initial hospitalization and rehospitalizations will be provided.

5.7.6. Invasive Intracranial Procedures

Invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications are found in Protocol Appendix G.

Number of procedures, and the number and proportion of participants with at least 1 of invasive intracranial procedures performed post-randomization will be summarized descriptively by treatment group and total. All surgeries and interventional procedures specifically intended to manage the hematoma and/or its complications will be tabulated.

5.7.7. Immunogenicity

Tabulations of immunogenicity results up to Day 30 (antibodies to FX, FXa, and andexanet, and neutralizing antibodies to FX, FXa, and andexanet) will be provided. A positive antibody response will be defined as a positive titer that occurs after baseline or an increase in titer from baseline to post-baseline. Baseline values are considered data captured within 120 minutes prior to randomization. Rates of antibody response to various antigens (andexanet, FX, and FXa) will be summarized by the dose of andexanet (high versus low) for the andexanet subset of Safety Set.

5.8. Subgroup Analyses

The following subgroup analyses will be performed for the primary endpoint on the ITT Set using the same stratified CMH test described in Section 5.3.1. For subgroups with < 5 participants, only summary statistics will be presented; a statistical inferential analysis will not be performed.

- Age (< 65 years, 65 to 74 years, or ≥ 75 years)
- Sex (male or female)
- Race (groups as collected on electronic case report form (CRF))
- Geographic region (North America, Europe, or Asia)
- Prior FXa inhibitor (apixaban, edoxaban, or rivaroxaban)
- Indication for prior FXa inhibitor (atrial fibrillation/flutter, venous thromboembolism including prevention and treatment, or other)
- Baseline anti-fXa activity (< 30 or ≥ 30 ng/mL)
- Baseline anti-fXa activity (< 75 or ≥ 75 ng/mL)
- Determination of the ICH score at baseline (< 3 or ≥ 3)
- Baseline volume of hematoma (< 30 or ≥ 30 mL)
- Baseline volume of hematoma (< 0.5 or ≥ 0.5 mL)

- Index bleeding location (ICrH-intracerebral hemorrhage , ICrH-intraventricular hemorrhage, intracranial-multicompartment, intracranial-subdural, and intracranial-subarachnoid)
- Time to randomization since the last FXa inhibitor dose (< 8 or ≥ 8 hours)
- Andexanet dose (high dose versus UC and low dose versus UC)
- UC received (andexanet vs PCC, andexanet vs non-PCC)

Forest plots of the treatment differences in the proportion of participants achieving effective hemostasis will be generated for the subgroup analyses on the ITT Set.

5.9. Interim Analyses

One planned, formal interim analysis on the primary efficacy endpoint will be performed by the DSMB-associated statistician after 50% of the anticipated participants has been adjudicated for hemostatic efficacy. DSMB will evaluate the results and recommend altering or stopping the study in the event of efficacy. Enrollment will not be paused during the interim analysis.

5.9.1. Stopping Criterion Due to Efficacy at Interim

The overall type I error for the interim and final analyses is controlled at 5% by employing the alpha spending function by Lan and DeMets based on Pocock boundaries (DeMets, 1994). If the interim p-value is < 0.0310 for comparing andexanet and UC in the primary endpoint analysis, DSMB may recommend stopping the study. In this case, the efficacy results from the interim analysis (with 50% of the anticipated participants) will be used for regulatory communication and submission. Enrollment of participants will proceed without interruption while the analysis is ongoing, resulting in > 50% of the anticipated participants in the final data cutoff; efficacy analysis on the final data cutoff will be considered as a sensitivity analysis.

5.9.2. Sample Size Re-estimation at Interim

If the DSMB recommendation at interim is to continue the study, a preplanned SSR will be performed by the DSMB-associated statistician with the interim data. The SSR will be based on a conditional power (CP) of comparing andexanet and UC at the final analysis (n=900), given the interim data, using a promising zone between 30% and 90% (Mehta, 2011). The assumption used for CP calculation is that the rate of hemostatic efficacy in andexanet and UC at the final analysis is 80% and 70%, respectively. Based on the observed CP, DSMB will recommend:

- No increase in the sample size, if the CP < 30% or > 90%
- An increase in the sample size to up to 1200, if 30% ≤ CP ≤ 90%

5.9.3. Primary Analysis if Study is Continued from Interim

When no change in the sample size occurs (ie, interim decision to keep the original planned sample size), the conventional CMH statistics will be used at the final analysis to determine statistical significance (Wassmer, 2016).

In contrast, if the total sample size is increased per interim analysis decision, then the final analysis will use the weighted statistic proposed by Cui, Hung, and Wang (1999).

In this case, the test statistic at the final analysis is a weighted sum of the test statistic at the interim analysis (Stage 1: n1 = 450), and the test statistics based on additional participants (Stage 2: n2 =750); the weight is 0.5 to avoid introducing bias. The weighted statistics is calculated as follows:

$$Z_{\mathrm{CHW}} = \sqrt{w}\, Z_1 + \sqrt{1-w}\, Z_2$$

where $w = 0.5$, Z_1 and Z_2 are the CMH test statistics at Stage 1 and Stage 2, respectively.

5.10. DSMB and Other Committees

Each of the planned study committees will have a charter outlining its activities and responsibilities. Interim monitoring of efficacy and safety data will be performed periodically by the DSMB as described in the DSMB charter. The DSMB may also recommend termination of the study for any safety concern that is felt to outweigh potential benefits.

In brief, the purpose of each committee is as follows:

- Independent EAC: The EAC will oversee the adjudication of effective hemostasis within the first 12 hours post-randomization. In addition, all TEs and deaths will be adjudicated. The EAC will remain blinded to treatment assignment for all participants. Details for the EAC are located in the EAC Adjudication Charter.
- Independent DSMB: The DSMB will monitor all safety and efficacy data, evaluate the interim analysis performed by the unblinded independent DSMB statistician, and make recommendations for study modification or stopping due to efficacy or safety reasons. Details for the DSMB are located in the DSMB Charter.

5.11. Handling of Laboratory Samples Out of Stability

If there are bioanalytical samples for assessing anti-fXa activity out of stability window due to reasons such as change in the bioanalysis provider, an additional analysis excluding samples out of stability windows may be performed to evaluate the impact of stability issue. This applies to the following analyses:

Secondary analysis for percent change from baseline to nadir in anti-fXa activity by ranked ANCOVA (Section 5.4)

Correlation analysis between effective hemostasis and percent change from baseline to nadir in anti-fXa activity 2 hours post-randomization (Section 5.5.7)

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to the analysis:

Defining the Per Protocol Set

The Per-Protocol Set (PPS) will include all participants in the ITT Set who did not have important protocol deviations impacting the primary hemostatic efficacy endpoint.

The reasons for exclusions and inclusion from the PPS will include the following subset of major protocol deviations:

- Inclusion/Exclusion:
  - Participant failed the following inclusion/exclusion:
    - Inclusion Criterion #3: An acute intracerebral bleeding episode of specified volume requirements
      - Even if the locally determined intracerebral bleed volume is out of per-protocol requirement, if subsequent average core lab screening volume assessment is within per-protocol requirements, then participant is eligible for PP set.
    - Inclusion Criterion #4: Performance of a head CT or MRI scan demonstrating the intracerebral bleeding within 2 hours prior to randomization
      - If CT/MRI scan is performed out-of-window/missing: If the EAC can determine an efficacy outcome, then participant is considered in PP set.
    - Inclusion Criterion #5: Specific treatment regimens and associated anti-fXa testing requirements with an FXa inhibitor
      - If central lab baseline/screening value collected within 2 hours of randomization or pre-treatment administration is >100ng/ml then participant is included into PP set
    - Inclusion Criterion #6: Where such timing is collected, time from bleeding symptom onset prior to the baseline imaging scan.
    - Inclusion Criterion #9: NIHSS score ≤ 35 at the time of consent (Protocol Amendment #2 only)
      - If NIHSS is performed out-of-window/missing: If the EAC can determine an efficacy outcome, then participant is considered in PP set.
    - Exclusion Criterion #1: Planned surgery affecting hematoma volume within 12 hours after randomization

- Exclusion Criterion #2: GCS score < 7 at the time of consent unless intubated and/or sedated for non-neurologic reasons <2 hours of consent
  - If GCS performed at informed consent is missing, then participant is excluded from PP set
  - Lack of evidence for intubation/sedation for non-neurological reason, then participant is excluded from PP set
  - If GCS is out-of-window; so long as the GCS documented is pre-treatment administration and >7, participant may be included into PP set.

- Exclusion Criterion #10 (PA #2) or #11 (PA #1, Original protocol): Receipt of restricted drugs or blood products within 7 days prior to consent
- Exclusion Criterion #11 (PA #2) or #12 (PA #1, Original protocol): Past use of andexanet (or planned use of commercial andexanet)
- Exclusion #13 (Original protocol, PA#1) or #12 (PA #2): Treatment of investigational drug <30 days prior to consent
- Exclusion Criterion #16: NIHSS Score >35 at time of consent (PA #1 only)
  - See appliable exceptions in section above 'Inclusion Criterion #9: NIHSS score ≤ 35 at the time of consent (Protocol Amendment #2 only)'

- Randomization:
  - The wrong study treatment is assigned post-randomization:
    - Use of pro-coagulant blood products or haemostatic agent for participant randomized to andexanet <3 hours post randomization where andexanet is not administered within 3 hours post randomization.
    - Use of andexanet for participant randomized to usual care <12hrs post randomization
  - Study treatment is given prior to randomization

- Investigational Product (Andexanet) Administration:
  - Missing dose or Treatment administered incorrectly:
    - Wrong bolus dose
      - Low andexanet bolus dose if < 360mg administered
      - High andexanet bolus dose if < 720mg administered
    - Wrong infusion dose
      - Low andexanet infusion dose if < 432mg administered

- High andexanet infusion dose if < 864mg administered

  - Start of bolus is >30 minutes after randomization and either >2 hours of baseline imaging scan or >6 hours of symptom onset
  - Start of infusion is >15 minutes after end of bolus
  - There is a mismatch between recommended andexanet dose regimen and actual dose administered such that:
    - Subject assigned high dose but receives low dose andexanet is excluded from PP set
    - Subjects assigned low dose but receives high dose andexanet are eligible for PP set.

- Procedural:
  - 12hr NIHSS assessments performed by assessor unblinded to participant's treatment allocation
  - Unless the EAC is able to determine hemostatic efficacy for affected participants, the following will render the participant not evaluable for the Per Protocol Set if EAC concludes the participant is 'Nonevaluable due to administrative reasons'.
    - NIHSS:
      - Missing NIHSS score at baseline and/or 12 hours post-randomization
      - Baseline NIHSS score is >2 hours prior to randomization or post-randomization
      - 12 hour NIHSS score is <11 hours or >13 hours post-randomization
      - Confounded assessments (eg crossover or due to sedation or intubation)
    - Imaging (CT or MRI):
      - Imaging is missing at baseline and/or 12 hours post-randomization
      - Baseline imaging is >2 hours prior to randomization or post-randomization
      - 12-hour imaging is <11 hours or >15 hours post-randomization
      - Confounded assessments (eg inconsistent imaging modality)

Effective Hemostasis

Effective hemostasis is assessed based on image evaluation (CT or MRI), NIHSS score, and use of rescue therapy and categorized into excellent, good, or poor/none. Imaging will be performed at baseline and 12 hours post-randomization and should utilize a consistent imaging modality for both time points to minimize technical discrepancy (ie, CT or MRI scan). NIHSS evaluation

(blinded or unblinded) to inform effective hemostasis will be performed at baseline (prior to randomization) and at 2, 3, 6, and 72 hours post-randomization. Blinded NIHSS evaluation will occur at 12 and 24 hours post-randomization. Use of rescue therapy (including procedures intended to treat the hematoma) between > 3 and < 12 hours post-randomization will be considered a treatment failure (ie, poor/none effective hemostasis).

Effective hemostasis will be further defined as follows:

- 1 = for participants with effective hemostasis rated as excellent/good
- 0 = for participants with effective hemostasis rated as poor/none

For a participant to have excellent or good effective hemostasis, he or she must meet all of the following criteria:

- An NIHSS score of less than +7-point change from the baseline score at 12 hours post-randomization
- An increase of no greater than 35% from baseline in hematoma volume between baseline and 12 hours post-randomization
- No rescue therapy received between 3- and 12-hours post-randomization

The majority of cases will not require review by adjudicators as the outcome rating will be obvious based on the core laboratory interpretation, NIHSS scores, and lack of additional treatments or procedures. An algorithm will be applied to the data from the imaging core laboratory and information provided by the sites on CRFs. The algorithm will determine if the case can be immediately classified as excellent, good, or poor/none or whether the case requires review by adjudicators and additional review by the EAC. Cases will be referred for EAC review, if the change in hematoma volume is < 35% and the change in the NIHSS score between baseline and 12 hours is < 7 and if one of the following criteria is met:

- baseline or 12-hour scans (11 to 15 hours post-randomization) missing, uninterpretable, or fall outside the collection window.
- NIHSS scores missing or fall outside the collection window for either baseline or 12-hour evaluations.
- Cases where the blinded imaging core laboratory readers indicate that review by the EAC is needed (or 3 readers disagree on classification of hematoma volume change).
- Cases where the participant was either sedated or intubated for either baseline or 12-hour NIHSS assessment (or both).
- Documented procedures that could potentially drain hematoma between 3- and 12-hours post-randomization.
- Cases, where it is determined that there is insufficient information or where it is not otherwise possible to properly assess the effect of treatment, will be further classified by the EAC as follows:
    - Nonevaluable due to administrative reasons (eg, follow-up scans not available/performed/interpretable and the participant transferred to another

facility for administrative purposes); these participants will be analyzed as having poor/none effective hemostasis.

- Nonevaluable due to clinical reasons (eg, the participant died and the participant had unplanned surgery draining hematoma); these participants will be analyzed as having poor/none effective hemostasis.

Identifying Rescue Medications/Procedures

Rescue medications are identified from the concomitant medication CRF pages based on the following:

1. If indication for medication is "TO ACHIEVE HEMOSTASIS FOR CONTINUOUS (WORSENING) INTRACEREBRAL HEMORRHAGE BLEED," "TO ACHIEVE HEMOSTASIS FOR INITIAL BLEED," or "TO ACHIEVE HEMOSTASIS FOR NEW BLEED RE-BLEED" (except for tranexamic acid, which is permitted regardless of indication).
2. If > 3 to < 12 hours post-randomization; if the time of the medication is missing, these are not considered to be rescue medications.

Rescue procedures are identified from the Procedure - Other CRF page based on the following:

1. Regardless of indication, if the following procedures, which definitely impact hematoma volume, are reported between > 3 and < 12 hours post-randomization, they are only considered rescue procedures if categorized as such for the EAC.
2. Such procedures include the following:
    a. Burr hole with evacuation/drainage of hematoma
    b. Burr hole for implanting ventricular catheter
    c. Craniectomy/craniotomy for evacuation/drainage of hematoma
    d. Craniectomy/craniotomy for decompression

Procedures performed within 3 to 12 hours, which may potentially impact hematoma volume, will be reviewed by EAC. These procedures include the following:

1. Cerebral endoscopy
2. Burr hole for other indications
3. Craniectomy/craniotomy for treatment of intracranial penetrating wound
4. Craniectomy/craniotomy for other indications
5. Surgical repair of intracranial arteriovenous malformation
6. Surgical repair of intracranial aneurysm

Other (if the site cannot reclassify to one of the procedural options, the EAC will determine if the procedure would impact effective hemostasis)

Handling of Missing Data for Adjudication of Effective hemostasis

The primary efficacy analysis, effective hemostasis, will be based on the ITT Set. If data supporting either the imaging or the clinical components of the adjudication of effective hemostasis are missing, they will be handled as follows:

- If the 12-hour scan is out of window (eg, performed at 6 or 18 hours), the EAC will determine whether an unscheduled scan is sufficient to be evaluated as a 12-hour scan. If not, then the scan will be considered missing.
- If the 12-hour scan is missing or uninterpretable, the EAC will determine whether the scan is missing/uninterpretable for administrative reasons (eg, investigator oversight and scheduling conflict with other participants) or clinical reasons (eg, the participant died and the participant went to surgery).
- If the 12-hour NIHSS is out of window (eg, performed at 6 or 18 hours), the EAC will determine whether the NIHSS is sufficient to be evaluated as a 12-hour NIHSS. If not, then the NIHSS assessment will be considered missing.
- If the 12-hour NIHSS score is missing or difficult to interpret (eg, discordance with imaging changes, large magnitude changes, or swings in value), the EAC will determine whether the NIHSS score is missing/difficult to interpret due to administrative reasons or clinical reasons.

Cases, where it is determined that there is insufficient information or where it is not otherwise possible to properly assess the effect of treatment, will be further classified by the EAC as "nonevaluable due to administrative reasons" (eg, follow-up scans not available/performed/interpretable and the participant transferred to another facility for administrative purposes) and handled as poor/none in the primary analysis or "nonevaluable due to clinical reasons" (eg, the participant died and the participant had unplanned surgery draining hematoma) and handled as poor/none in the primary analysis.

Handling of Data for Missing Anti-fXa Activity

Values > 950 ng/mL will be replaced with 950 ng/mL (the upper limit of quantitation). Values < 4 ng/mL will be replaced with 4 ng/mL (the lower limit of quantitation). In addition, other values identified as ">", "≥", "<", or "≤" will be replaced with the actual values (eg, > 750 will be replaced with 750). For missing baseline measurements, if any baseline measurement collected outside of visit window is available, then the missing baseline value will be replaced with the out-of-window measurement.

Handling of Data for Thrombin Generation

ETP values identified by the laboratory as below measurement capacity will be replaced with zeros.

Concomitant Medications/Procedure With Partial or Missing Dates

The use of concomitant medications allowed in the study are found in Protocol Section 7.2. Concomitant medications are medications that are started on or after the start of study treatment or are ongoing at the start of study treatment. For participants who are randomized into the UC

arm and received no treatment, their randomization date is used as the start of study treatment. If the start date of a medication is partially or completely missing and the end (stop) date and time of the medication does not indicate that it occurred prior to first dose, then the medication will be considered as both prior and concomitant if either type cannot be determined with certainty.

The following imputation rules apply after the above concomitant and prior rules have been followed:

- For start date: If the day is missing, then impute with 01, and if both the day and the month are missing, then impute with 01-Jan.
- For end date: If the day is missing, then impute with the last day of that month, and if both the day and the month are missing, then impute with the last visit/contact/survival/death day of study or Day 30.
- If the year is missing, then keep as is. No imputation is required if the complete date is missing.

Definition of Baseline Values

Baseline is defined as the most recent nonmissing assessment within the protocol-defined visit window prior to randomization. If there is no assessment within the visit window of randomization, then the assessment closest to randomization prior to treatment will be used as baseline. Data that are outside the baseline assessment windows specified above will not be excluded from analyses but will be identified as protocol deviations.

Start of Study Treatment

For andexanet treatment group, the start of study treatment will be the start of andexanet. For the UC treatment group, the start of study treatment will be the start of the specific UC drug received by the participant, or if the UC consists of no treatment, then the start of study treatment will be the randomization date for the participant.

Restart of Anticoagulants

The time when anticoagulants were restarted is defined as (date restart anticoagulation - date of the first study treatment) + 1. If the participant is assigned to UC and receive no treatment, then the date of the first study treatment will be replaced by the date of randomization. Oral anticoagulants will be summarized separately.

Study Day

For participants who are randomized to UC group and received no treatment, the study day is calculated based on randomization date. For events prior to randomization, the study day is calculated as date of event - date of randomization; for events on or after randomization, the study day is calculated as date of event - date of randomization + 1. For other participants, the study day is calculated based on the date of treatment initiation, using the same formula as above. Study day is referred as “day” in outputs.

Calculation of On Treatment Nadir

On treatment nadir is the minimum anti-fXa activity post-randomization (ie, value observed at either 1- or 2-hour post-randomization evaluation). A percent reduction will be calculated as the ratio between the maximum reduction from baseline and the baseline value, multiplied by 100.

Length of Hospitalization and Rehospitalization

The following steps will be followed to calculate the length of hospitalization (or rehospitalization):

- The length of stay (LOS) will be calculated as discharge date/time - admission date/time + 1.
- If the participant admission time and the discharge time are missing and the dates are the same, the LOS will be assumed to be 1 day.
- If the participant admission time and the discharge time are missing and the dates are not the same, the LOS will be calculated using the date portion of the dates plus 1.
- If the discharge date is missing and there is no new admission date, the date of the 30-day visit or the date of death (whichever is earlier) will be imputed as the discharge date.
- If the participant has withdrawn consent, the discharge date will be imputed as the date of the 30-day visit or the date of death (whichever is earlier and/or available).

Neurologic Deterioration at 24 hours

Neurologic deterioration at 24 hours is defined as an NIHSS increase ≥ 4 at 24 hours compared to baseline or a GCS score decrease ≥ 2 at 24 hours compared to baseline.

Neurologic Deterioration at 12 hours

Neurologic deterioration at 12 hours is defined as an increase of ≥ 7 point from baseline to 12 hours in NIHSS.

Utility-Weighted mRS

Mean utility values will be based on EQ-5D-5L at the same visit and will be determined by averaging the utilities of all participants within each mRS category.

AEs With Partial or Missing Start and End Date

If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE do not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first dose, then the AE is treatment emergent.
- If the start year is the same as the year of the first dose and:
    - If the start month is missing, then the AE is treatment emergent.
    - If the start month is present and is the same as or after the month of the first dose, then the AE is treatment emergent.

- If the start date is completely missing, then the AE is treatment emergent.

If both start and end dates of AEs are completely missing, no imputation will be performed, and those AEs will be considered treatment emergent.

If the start date is partial:

1. If only the day is missing:
    a. If the month/year of the start date is the same as those of the first study drug administration date, then the missing day will be imputed as the smaller nonmissing value of (day of first study drug administration, day of the AE end date).
    b. Otherwise, impute the missing day as "01."
2. If both day and month are missing:
    a. If the year of the AE start date coincides with the year of the first study drug administration date, the partial start date will be set as the first study drug date. If this leads to a date after the AE end date, then the missing day and month of the AE start date will be imputed as the day and month of the AE end date.
    b. If the year of the AE start date is different from the year of the first study drug administration date, the missing day and month of the AE start date will be imputed as "01" and "01."

If the start date of an AE is the same as the first study drug administration date but the time is missing, the AE is treatment-emergent.

If the stop date is partial:

1. If only the day is missing:
    a. The missing day will be imputed as the last of the month, adjusting for the leap year.
2. If both day and month are missing:
    a. If the year of the AE end date coincides with the maximum of (the year of first study drug administration date or the year of the last study drug administration), then the missing month will be imputed as the month of the corresponding study drug administration date (first or last) and the missing day will be imputed as the last of the month adjusting for the leap year.
    b. Otherwise, the missing day and month of the AE stop date will be imputed as "31" and "12."

Adverse Event of Special Interest (AESI)

The AESI in this study is thrombotic events based on adjudication. The EAC adjudicate TEs or potential TEs based on AE review to include the following: stroke (or cerebral vascular accident), transient ischemic attack, deep vein thrombosis, pulmonary embolism, arterial systemic embolism, and myocardial infarction. For the purposes of adjudication, a "thromboembolic event" is to be considered synonymous with a "TE." Detailed definitions of TEs, as well as AE terms that require adjudication to determine if definitions for a TE are met, are provided in the Adjudication Charter.

Clinically Significant Laboratory Test Abnormalities

Table 5 shows the following clinically significant criteria that will be followed. Additional criteria may be applied.

Table 5: Clinically Significant Abnormality Criteria

Laboratory Parameter	Criteria for Clinical Significance
Alkaline phosphatase	≥ 3× ULN
Alanine aminotransferase	≥ 3× ULN
Aspartate aminotransferase	≥ 3× ULN
Bilirubin	≥ 34.2 µmol/L
Blood urea nitrogen	≥ 10.71 mmol/L
Creatinine	≥ 176,8 µmol/L
Eosinophils/leukocytes	≥ 10%
Hematocrit	Female: ≤ 32% AND ≥ 3% decrease from baseline Male: ≤ 37% AND ≥ 3% decrease from baseline
Hemoglobin	Female: ≤ 95 g/L Male: ≤ 115 g/L
Neutrophils/leukocytes	≤ 15%
Platelet	Low: ≤ 75 × 10^9/L High: ≥ 700 × 10^9/L
Uric acid	Female: ≥ 505.59 µmol/L Male: ≥ 624.54 µmol/L
Leukocytes	Low: ≤ 2.8 × 10^9/L High: ≥ 16 × 10^9/L

Abbreviation: ULN = upper limit of normal

Clinically Significant Vital Sign Abnormalities

The following clinically significant criteria will be followed:

Table 6: Clinically Significant Vital Sign Criteria

Vital Sign Parameter	Criteria for Clinical Significance
Temperature	< 36.4 ºC or > 38.5 ºC
Respiratory rate	< 12 or > 40 breaths/min
Heart rate	< 40 or > 160 bpm
Systolic blood pressure	< 70 or > 180 mmHg

Diastolic blood pressure	< 40 or > 120 mmHg

Identifying Past Medical History for Select Diagnoses

The following dictionary-derived terms will be used to identify medical history for purposes of the subgroup analyses:

1. Atrial fibrillation
2. Cardiac failure congestive
3. Cerebrovascular accident
4. Chronic kidney disease
5. Diabetes mellitus
6. Hypertension
7. Transient ischemic attack/stroke
8. Neoplasm malignant
9. Deep vein thrombosis
10. Thromboembolism
11. Pulmonary edema

6.2. Appendix 2: Study and Participant Characteristics

Summaries that are presented as the Table 14.1 or Table 14.3 series, which are not described in the body of the SAP are provided here.

6.2.1. Protocol Deviations

Protocol deviations will be tabulated by treatment group and total. By-participant listings of protocol deviation data will be provided. For details, please refer to the protocol deviation review plan.

6.2.2. Demographics and Disease Characteristics

Baseline and demographic characteristics will be summarized by treatment group.

By-participant listings of demographics, baseline characteristics, initial bleeding events, events leading to randomization, medical/surgical history, and prior/concomitant medications will be provided.

6.2.2.1. Demographics and Disease Characteristics (Bleeding)

The following demographic and baseline disease characteristics variables will be summarized by treatment group and total using descriptive statistics. No inferential analyses of these data are planned.

- Sex (male or female).

- Race (American Indian or Alaska native, Asian, Black or African American, Native Hawaiian or other pacific islander, White, or other).
- Ethnicity (Hispanic or Latino, not Hispanic Or Latino, not reported, or unknown).
- Age (< 65 years, 65 to 74 years, or ≥ 75 years).
- Height (cm).
- Weight (kg).
- Body mass index (< 25 kg/m^2, 25 to < 30 kg/m^2, or ≥ 30 kg/m^2).
- Tobacco use (current, former, or never).
- Geographic region (North America, Europe, or Asia).
- FXa inhibitor (apixaban, edoxaban, or rivaroxaban).
- Indication of FXa inhibitor (atrial fibrillation, venous thromboembolism, or other).
- Intended UC agent: PCC, other
- Time since the last FXa inhibitor dose to scan for bleeding (< 180 minutes versus ≥ 180 minutes).
- Baseline anti-fXa activity (< 30 to ≥ 30 ng/mL and < 75 to ≥ 75 ng/mL).
- Participant presentation location (emergency room/department, ICU, inpatient ward, stroke clinic, transfer from outside hospital, or other).
- Approximate hematoma volume of baseline CT/MRI (< 30 and ≥ 30 mL; < 0.5 and ≥ 0.5 mL).
- Mechanism of injury (spontaneous ICrH and trauma ICrH); participants who will not have bleeding as a result of trauma will be considered as spontaneous bleeding.
- Time from hospitalization to study treatment.
- Time from the last FXa inhibitor dose to treatment (< 8 or ≥ 8 hours).
- Time from symptom onset to baseline CT or MRI scan (< 180 minutes versus ≥ 180 minutes).
- Time from CT or MRI scan to treatment.
- Time from bleeding to treatment onset.
- Primary bleeding location per adjudication (intracerebral hemorrhage, not intracerebral hemorrhage, and multicompartment, where intracerebral hemorrhage includes intracerebral or intraventricular bleeding, and not intracerebral hemorrhage includes subdural or subarachnoid bleeding).
- Intracerebral hemorrhage (ICH) score (< 3 or ≥ 3).

6.2.2.2. Medical/Surgical History and Baseline Physical Examination

The number of participants with any medical history will be tabulated by treatment group and total. The number of participants with at least 1 medical history will also be tabulated by SOC and PT; if participants experienced > 1 history in a specific SOC or PT, they will be counted only once for the SOC or PT.

6.2.3. Prior and Concomitant Medications

Prior medications are defined as medications that are started prior to the start of study treatment, as defined in Section 6.1.

Concomitant medications are defined as medications that are started on or after the start of study treatment or are ongoing at the start of study treatment. Prior medications with missing end dates will be counted as concomitant.

The number of participants with any prior and concomitant medications will be tabulated by treatment group and total. The number of participants with at least 1 prior and 1 concomitant medications will also be tabulated by Anatomical Therapeutic Chemical 3 Classification and by generic name. All prior and concomitant medications will be listed and summarized by treatment group for the Safety Set.

In addition, the number of participants of concomitant anticoagulants and antiplatelet drugs will be tabulated by treatment group and total.

6.3. Appendix 3: Instrument Scoring Details

6.3.1. Glasgow Coma Scale

In order to provide a total summary score for the GCS, data coded as “untestable” for the verbal response question will be coded as follows based on the combination score of eye and motor (EM) scores (Brennan, 2020):

- If the EM scores are 2 to 6, then add 1.
- If the EM score is 7, then add 2.
- If the EM score is 8 or 9, then add 4.
- If the EM score is 10, then add 5.

6.3.2. Utility-Weighted mRS

The determination of utility weights for the mRS will be determined as follows:

- mRS utilities represent preferences for mRS health states and range from < 1 to 1 (perfect health), where 0 indicates death.
- Utility values for each mRS health data will be elicited using the EQ-5D-5L responses of participant or proxy assessed at 30 days post-randomization (Chaisinanunkul, 2015). The EQ-5D-5L consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels each (no

problems, slight problems, moderate problems, severe problems, and unable to/extreme problems), thus defining 3125 distinct health states.

- Converting the EQ-5D-5L responses into EQ-5D utility values was done according to Table 7 below. Participants who died before the follow-up interviews at 30 days will receive a utility value of 0. The utility values range from < 0 (where 0 is the value of a health state equivalent to dead, and negative values represent values as worse than dead) to 1 (full health).
- The utility weights for each mRS category (1 to 5, excluding 6 which is death) will be determined by averaging the derived EQ-5D utilities of all participants within each of the mRS health states (eg, the utility weight for mRS = 1 is the average of the utilities of all participants with mRS = 1).
- The utility weights as derived above will be used in analyses.

6.3.3. EQ-5D-5L Health State Index Score Calculations

The responses to the 5 EQ-5D dimensions can be converted into a single number called an index value. The EQ-5D-5L health state index score is derived by applying a formula that attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by subtracting the appropriate weights for each dimension level of health state from 1. The EQ-5D-5L index scores for this study will be obtained using the US composite time trade-off method (Pickard, 2019; Mehta, 2011). The calculation is illustrated in below (Pickard, 2019):

Table 7: EQ-5D-5L US cTTO Value Set

US cTTO		Example: The value for health state is 21354
Full health (11111)		Full health = 1
Mobility Level 2	-0.096	-0.096
Mobility Level 3	-0.122	
Mobility Level 4	-0.237	
Mobility Level 5	-0.322	
Self-care Level 2	-0.089	0
Self-care Level 3	-0.107	
Self-care Level 4	-0.220	
Self-care Level 5	-0.261	
Usual activity Level 2	-0.068	
Usual activity Level 3	-0.101	-0.101

Table 7: EQ-5D-5L US cTTO Value Set

US cTTO		Example: The value for health state is 21354
Usual activity Level 4	-0.255	
Usual activity Level 5	-0.255	
Pain/discomfort Level 2	-0.06	
Pain/discomfort Level 3	-0.098	
Pain/discomfort Level 4	-0.318	
Pain/discomfort Level 5	-0.414	-0.414
Anxiety/depression Level 2	-0.057	
Anxiety/depression Level 3	-0.123	
Anxiety/depression Level 4	-0.299	-0.299
Anxiety/depression Level 5	-0.321	
Health state index score		=1 - 0.096 + 0 - 0.101 - 0.414 - 0.299 = 0.090

Abbreviation: cTTO = composite time trade-off; EQ-5D-5L = European Quality of Life 5-Dimension 5-Level; US = United States

6.4. Appendix 4: Additional Details on Statistical Methods

6.4.1. COVID-19 Vaccine Risk Assessment

6.4.1.1. Vaccination

Following a review of the available coronavirus disease 2019 (COVID-19) vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca, and Johnson & Johnson), it is unlikely that the immune response to a COVID-19 vaccine (and therefore the efficacy of the vaccination) would be diminished with concomitant administration of andexanet, based on andexanet's mechanism of action. There is currently no available information evaluating the safety and efficacy of COVID-19 vaccines in participants treated with andexanet.

6.4.1.2. Potential Risks and Mitigation Measures

Acute intracerebral hemorrhage can cause irreversible morbidity and even mortality if untreated. As such, and because existing treatment options may be less effective than andexanet, the benefit a participant may receive from joining this investigational study is potentially significant. The potential risks and mitigation measures put in place considering the COVID-19 pandemic are

provided in Protocol Section 3.5.1, which should be taken into consideration by the Principal Investigator at site to for participants.

6.4.1.3. Reason for Not Collecting COVID-19 Information

Participants afflicted with intracranial bleeding resulting from trauma or sudden onset focal neurologic deficit (ie, hemorrhagic stroke) are unlikely to defer/delay their attendance into the hospital (unlike outpatient follow-up for chronic/subacute conditions). The presenting clinical condition is usually severe enough to warrant emergency presentation to the hospital. Furthermore, once the diagnosis is confirmed and treatment is initiated, the clinical management and standard of care of participants for the index bleed would not differ for all acute treatments (including those within the first 24 to 72 hours) administered as in-participant. In addition, participant follow-ups at Study Days 7 and 14 may be undertaken by telephone.

ANNEXA-I protocol excludes participants with severe sepsis or septic shock at the time of randomization. If a participant was acutely unknowingly unwell with COVID-19 respiratory infection, this may restrict their inclusion into the study.

There has been evidence of COVID-19-associated thrombotic complications requiring temporary anticoagulation, and WHO put direct oral anticoagulants on the list of emergency medicines for COVID-19. However, there does not appear to be a corresponding increase in bleeding rates for participants who are anticoagulated, as anticoagulation practices vary substantially across and within countries and are usually short term (1 to 2 months) where needed.

In summary within the conditions set by our eligibility criteria, COVID-19 is unlikely to have altered participants' clinical presentation for in, impacting the validity of the study; participant response to andexanet, which has specific mechanism of action targeting FXa inhibitor; participant response to vaccine after andexanet exposure; and participant-associated intracerebral hemorrhage clinical management. There is a chance a participant experiences COVID-19 infection post-enrollment; this episode and its outcome would be captured as an AE and administration of treatment (including vaccination) would be documented as concomitant medications.

6.5. Appendix 5: Changes to Protocol-Planned Analyses

The definition of enrolled set is updated in SAP as all participants who signed an informed consent form, excluding screen failures.

6.6. Appendix 6: List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CP	Conditional Power

Abbreviation	Definition
CRF	Case Report Form
CT	Computed Tomography
CV	Cardiovascular
DCO	Data Cutoff
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
EM	Eye And Motor
EQ-5D	European Quality Of Life 5-Dimension
EQ-5D-5L	European Quality Of Life 5-Dimension 5-Level
ETP	Endogenous Thrombin Potential
fX	Factor X
FXa	Factor Xa
GCS	Glasgow Coma Scale
ICrH	Intracranial Hemorrhage
ICU	Intensive Care Unit
ITT	Intent-To-Treat
IV	Intravenous
LOS	Length Of Stay
LS	Least Squares
MedDRA	Medical Dictionary For Regulatory Activities
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes Of Health Stroke Scale
PA	Protocol Amendment
PCC	Prothrombin Complex Concentrate
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SSR	Sample Size Re-Estimation
TE	Thrombotic Event

Abbreviation	Definition
TEAE	Treatment-Emergent Adverse Event
TFPI	Tissue Factor Pathway Inhibitor
UC	Usual Care
WBC	White Blood Cell
WHODrug	World Health Organization Drug Dictionary

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