9. STATISTICAL METHODS INTERIM ANALYSIS PLAN

- 19-515 Addendum to Statistical Analysis Plan_8Apr2022
- 19-515 Statistical Analysis Plan v1.0_24Sep2021

ADDENDUM TO STATISTICAL ANALYSIS PLAN

Version Number: 1.0

Protocol Title: Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Require Urgent Surgery (Annexa-S)

Protocol Number: 19-515

Protocol Amendment Number: 2

Compound: ALXN2070 (Andexanet Alfa)

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

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Addendum Version Date: 8 APR 2022

APPROVAL SIGNATURES

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11-Apr-2022 | 03:14 EDT

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The changes to the above signed statistical analysis plan (SAP) pertaining only to summary tables (i.e., data will still be provided in listings as appropriate) are as follows, and are a result of terminating the study after the enrollment of only 10 participants:

1. Section 4: Analysis Sets: The Per Protocol Set has been removed from all analyses.

2. Section 5.1: General Considerations: Confidence intervals (CIs) will no longer be provided for any descriptive statistics.

3. Section 5.3.2: Main Analytical Approach: The exact Clopper Pearson 95% CI for the proportion of participants with effective hemostasis will no longer be provided.

4. Section 5.3.3: Sensitivity Analysis: This analysis will no longer be performed on the Per Protocol Set, but will be performed on the Efficacy Set.

5. Section 5.4.2: Main Analytical Approach: The secondary endpoint will no longer be assessed with a 2-sided 95% non-parametric CI for the median.

6. Section 5.4.3: Sensitivity Analysis: This section is removed as the analysis described in Section 5.4.2 of the statistical analysis plan will not be repeated using the Per Protocol Set.

7. Section 5.5: Exploratory Endpoint Analysis: The following exploratory efficacy endpoints will no longer be analyzed:

    a. Relationship between intraoperative hemostasis and anti-fXa activity
    b. Reversal of anticoagulant effect as measured by thrombin generation (TG) parameters (with endogenous thrombin potential [ETP] as the primary measure)
    c. Occurrence of receiving 1 or more red blood cell (RBC) transfusions from start of the andexanet bolus through 12 hours after the end of surgery
    d. The number of RBC units transfused per participant from the start of the andexanet bolus through 12 hours after the end of surgery
    e. The use of non-RBC, non-platelet blood products and/or hemostatic agents (both system and topical) through 12 hours after the end or surgery
    f. Observed amount of intraoperative blood loss
    g. Difference between observed blood loss and predicted blood loss
    h. Transfusion corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery
    i. Time from the signing of informed consent to the start of surgery
    j. Time from clinical presentation at treatment facility to the start of surgery
    k. Length of index hospitalization, assessed at the Day 30 Visit
    l. Time from hospitalized in a post-anesthesia care unit (PACU) assessed at the Day 30 Visit
    m. Time hospitalized in an intensive care unit (ICU), assessed at the Day 30 Visit
    n. Length of surgery

o. Total time in the operating room (OR)
p. Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post-enrollment)
q. Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria, within 12 hours after the start of the initial surgery
r. Occurrence of re-operations for bleeding, including for surgical wound hematomas, within 12 hours after the end of the initial surgery
s. Change from baseline in tissue factor pathway inhibitor (TFPI) activity post-administration of andexanet
t. Change from baseline in anti-IIa activity (only participants taking enoxaparin)

Removal of these endpoints also involves removal of applicable sections in the SAP (sections 5.5.1: Relationship Between Anti-fXa Activity and Hemostasis, 5.5.3: Reversal of Anticoagulant Effect – Thrombin Generation, 5.5.4: Blood Product Usage, 5.5.5: Intraoperative Blood Loss, 5.5.6: Transfusion Corrected Change in Hemoglobin, 5.5.57: Healthcare Encounter and Surgical Intervention, 5.5.8: Post-surgical Major Bleeding, 5.5.9: Tissue Factor Pathway Inhibitor (TFPI), and 5.5.10: Anti-IIa Activity.

8. Section 5.5.2: Anti-fXa Activity – Absolute and Percent Change from Baseline: 95% CIs will no-longer be provided. Additionally, the tabulation of patients with percent reduction from baseline at time point >80% (and 95% CI) will also no-longer be provided.

9. Section 5.6: Safety Analyses: We will no-longer analyze the following:

    a. Thrombotic Events (TEs) within 30 days of enrollment, including those suspected and confirmed by adjudication
    b. Centrally adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality
    c. Antibodies to FX, FXa, and andexanet

10. Section 5.6.2.2: TEAEs and SAEs by System Organ Class (SOC) and Preferred Term (PT): We will no-longer provide tables summarizing treatment-emergent adverse events (TEAEs) by surgery type and baseline FXa inhibitor. Additionally, TEAEs and treatment-emergent related adverse events (AEs) will no-longer be tabulated at the PT level only. Furthermore, there will no-longer be a separate tabulation of TEAEs ≥5%.

11. Section 5.6.2.5: Deaths, Other SAEs, and Other Significant Adverse Events: The following will no-longer be analyzed:

    a. Events leading to death which were COVID-19 related
    b. Survival status reported by phone on the Day 30 or End of Study visit
    c. Deaths assessed by the event adjudicating committee (EAC)
    d. Deaths through the 30 Day Follow-up Visit by reason for death (Cardiovascular, non-cardiovascular)

12. Section 5.6.2.6: Adverse Events of Special Interest (AESIs): These analyses are to be removed.

13. Section 5.6.4: Vital Signs and Weight: The number of participants having clinically significant vital signs at each visit will no-longer be tabulated.

14. Section 5.7.2: Subgroup Analyses: Subgroup analyses will no-longer be performed.

15. Section 6.2.1: Protocol Deviations: Protocol deviations will no-longer be tabulated.

16. Section 6.2.2: Demographics, Baseline Characteristics, and History: Baseline and demographic characteristics will no-longer be summarized for the Efficacy Set. Additionally, COVID-19 diagnosis will no-longer be summarized for the Safety Set.

17. Section 6.2.3: Medical/Surgical History and Baseline Physical Examination: Baseline physical examination will not be tabulated.

18. Section 6.2.5: COVID-19 Impact: The number of participants with any number of visits missed or modified due to exposure to, or diagnosis of COVID-19 will no-longer be tabulated.

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TITLE PAGE

STATISTICAL ANALYSIS PLAN

Version Number: 1.0

Protocol Title: Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Require Urgent Surgery (Annexa-S)

Protocol Number: 19-515

Protocol Amendment Number: 2

Compound: ALXN2070 (Andexanet Alfa)

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Author: PPD

Version Date: 24 Sep 2021

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study 19-515 is based on Protocol Amendment 2, dated 20 Jul 2020.

SAP Version	Version Date	Change	Rationale
1.0	24 SEP 2021	Not applicable	Original version

APPROVAL SIGNATURES

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PPD

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PPD

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PPD, Medical Director — Date dd Mmm yyyy

1. INTRODUCTION

This Statistical Analysis Plan describes the final statistical methods for analyzing efficacy and safety data for Protocol "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)". Standard data presentation instructions, and table, figure, and listing specifications are contained in the Data Presentation Plan (DPP) in a separate document.

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 requiring urgent surgery. Additional information obtained from this study will include the adequacy and duration of andexanet dosing.

The attributes of the estimands (treatment, population, variable, intercurrent event, and summary measure) corresponding to the primary and secondary efficacy endpoints are summarized in Table 1 as follows:

Table 1: Objectives, Endpoints, and Estimand Attributes

Objective	Endpoints and Corresponding Estimand Attributes
Primary	
• To evaluate hemostatic efficacy following andexanet alfa treatment	Primary endpoint: Achievement of effective hemostasis (binary outcome) • Treatment: Andexanet • Population: Efficacy Set • Variable: Hemostasis (Effective/Ineffective) o Effective: intraoperative hemostasis = excellent/good o Ineffective: intraoperative hemostasis = moderate/poor • Intercurrent Events: o Participants whose hemostatic efficacy is 'non-evaluable due to clinical reasons' (according to the Endpoint Adjudication Committee [EAC] charter and adjudicated as such by the EAC) will be treated as ineffective hemostasis o Participants whose hemostatic efficacy is 'non-evaluable due to administrative reasons' (according to the EAC charter and adjudicated as such by the EAC) will be treated as not having an effective hemostasis value • Summary Measure: Proportion of patients achieving effective hemostasis
Secondary	
• To evaluate the effect of andexanet on anti-fXa activity	Secondary endpoint: Percent change in anti-fXa activity from baseline to evaluation period nadir • Treatment: Andexanet • Population: Efficacy Set • Variable: Percent change in anti-fXa activity from baseline to the nadir for the evaluation period from the end of the andexanet bolus to the end of the andexanet infusion

Objective	Endpoints and Corresponding Estimand Attributes
	• Intercurrent Event: Missing on-treatment nadir value will be treated as 0% change from baseline in anti-fXa activity • Summary Measure: Median percent change in anti-fXa activity from baseline to on-treatment nadir

Other endpoints are described in Section 5.5.

1.2. Study Design

This is a Phase 2 multicenter, prospective, open-label, proof-of-concept study of andexanet alfa (referred to subsequently as "andexanet"), with the objectives of determining the efficacy and safety of andexanet in participants who require urgent surgery (must occur within 12 hours of consent) who have, within 15 hours prior to surgery, received 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Approximately 100 participants will be enrolled. The duration of the study for any individual participant will be up to 37 days.

The start of surgery must be within 15 hours following the last dose of FXa inhibitor. If the time from last dose of FXa inhibitor is unknown or greater than 15 hours, participants with a local laboratory anti-fXa activity level obtained within 2 hours prior to consent > 100 ng/mL (> 0.5 IU/mL for participants taking enoxaparin) may be enrolled. Participants enrolled in this manner should receive a high-andexanet dosing regimen. In such cases, the start of surgery must begin no greater than 4 hours after the blood collection for the local test. The prespecified time periods and/or anti-fXa activity levels are designed to ensure participants have sufficiently high anti-fXa activity levels.

Participants will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Participants will receive an intravenous (IV) bolus of andexanet administered over approximately 15 to 30 minutes (depending on dose), followed immediately by an IV continuous infusion of andexanet for 2 hours, irrespective of the duration of surgery. The bolus must be completed immediately prior to the start of surgery (ie, at the first incision; designated as Time 0). The infusion should continue from prior to the start of surgery (initial skin incision) until the end of surgery (close of skin incision, or, if skin closure is not completed by intention, an equivalent milestone such as, dressing or packing the surgical incision). If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes). Additional andexanet, be it for extended treatment or re-dosing, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or postoperative complications are met (see Protocol Section 6.2).

The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the investigator's assessment of intraoperative hemostasis using a pre-specified 4-point scale and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC) (Section 5.3.1).

In addition to hemostatic efficacy, the EAC will adjudicate all deaths, thrombotic events (TEs), and post-surgical major bleeding events (eg, surgical hematomas). The EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review study

data once the 30-day visit is completed for the participant recruitment of approximately 33 and 66 participants.

All adverse events (AEs), including serious adverse events (SAEs), and survival will be followed through the Day 30 Post-treatment Visit.

See Section 6.7 for Schedule of Events and the protocol for additional details.

2. STATISTICAL HYPOTHESES

No hypothesis testing will be conducted in this single-arm, proof-of-concept study.

3. SAMPLE SIZE DETERMINATION

Approximately 100 participants will be enrolled. After accounting for 20% attrition (eg, canceled surgeries, discontinued and/or non-evaluable participants, or baseline anti-fXa activity analyzed by central laboratory less than the evaluability threshold), a sample size of 80 participants will provide an estimate of the proportion of achieving effective (excellent or good) hemostasis with a margin of error (half width of the 95% confidence interval [CI]) that is less than 11%.

4. ANALYSIS SETS

Four analysis sets will be used for the study: Enrolled Set, Safety Set, Efficacy Set (referred respectively as the Enrolled Population, Safety Analysis Population, and Efficacy Analysis Population in Section 11.3 of the protocol), and Per Protocol Set.

Analysis Set	Description
Enrolled Set	The Enrolled Set will consist of all participants enrolled (signed informed consent and met inclusion/exclusion criteria) into the study irrespective of whether they received andexanet or not.
Safety Set (SS)	The Safety Set will consist of all participants enrolled and treated with any amount of andexanet.
Efficacy Set	The Efficacy Set will include all enrolled participants who receive any amount of andexanet treatment, undergo surgery, and have a baseline anti-fXa activity analyzed by central laboratory at or above the evaluability threshold (75 ng/mL for apixaban and rivaroxaban, 40 ng/mL for edoxaban, and 0.25 IU/mL for enoxaparin).
Per-Protocol Set (PPS)	The Per Protocol Set will include all participants meeting the definition of the Efficacy Set with no important protocol deviations that could potentially impact the accuracy/interpretability of the primary or secondary efficacy endpoints. The Per Protocol Set exclusion criteria will be finalized prior to database lock.

5. STATISTICAL ANALYSES

5.1. General Considerations

For continuous variables, the number of observations, mean, median, standard deviation, first quartile (Q1), third quartile (Q3), interquartile range (IQR), and minimum and maximum values, will be presented. For categorical variables, unless specified otherwise, counts and percentages will be based upon number of participants with non-missing values in the analysis set.

Confidence intervals will be provided for the mean for all continuous efficacy variables except for percent change from baseline variables, for which CIs for the median will be generated. For binary variables, normal-approximated CIs for the binomial proportion will be provided unless stated otherwise.

No hypothesis testing will be conducted in this single-arm, proof-of-concept study. All CIs will be 2-sided and reported at the 95% confidence level unless stated otherwise.

Summary statistics will be provided for each time point/visit at which the variable is collected unless otherwise stated. Visit/time point windows will not be employed. See Section 6.7 for the schedule of study activities.

Summary table(s) will be generated for all data described in this SAP unless otherwise noted. At a minimum, data listings will be provided for these data.

In general, no missing data imputation will be performed unless stated otherwise.

It is anticipated that statistical summaries 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

The number of participants screened, and the number and percentage of screen failures along with the reason for screen failure will be reported, where screened participants are those who signed the informed consent.

The number of enrolled participants (Total), and the number of participants in the Safety and Efficacy Analysis Sets will be tabulated. Within each analysis set, the number of participants excluded from the Enrolled Set, along with the reason for exclusion will be tabulated.

Enrollment by region (North America, European Union, and Asia), country, and site will be tabulated for the Enrolled Set. Additionally, participant enrollment by protocol version will be tabulated. Finally, the number of participants who failed inclusion/exclusion criteria will be tabulated and along with the protocol version under which the failure occurred.

An accounting of study participant disposition will be tabulated for the Enrolled Set and will include the number of participants who completed the study (including the 30-Day Follow-up Visit), discontinued early, and the reason for discontinuation from the study. Descriptive statistics will be provided for study duration (days).

5.3. Primary Endpoint Analysis

The primary endpoint analysis will be performed on the Efficacy Set unless stated otherwise.

5.3.1. Endpoint

The primary efficacy endpoint is the achievement of effective hemostasis, as determined by the investigator's assessment of intraoperative hemostasis using a pre-specified 4-point scale (Table 2) and confirmed by adjudication by an independent EAC.

Table 2: Intraoperative Hemostasis Categories

Category	Definition
Excellent	Normal hemostasis during the procedure
Good	Mildly abnormal hemostasis as judged by quantity or quality of blood loss (eg, slight oozing from surgical wounds)
Moderate	Moderate abnormality in intraprocedural hemostasis (eg, controllable bleeding) but no need for additional systemic procoagulant products *
Poor	Severe hemostatic abnormality during the procedure (eg, severe refractory hemorrhage) and need for additional systemic procoagulant products *

* Tranexamic acid excluded.

The hemostasis evaluation would exclude unexpected blood loss due to surgical complications that may cause uncontrolled bleeding, such as unintended injury of a major vessel or parenchymal tissue.

For each participant, hemostasis will be considered to be effective if the intraoperative hemostasis category is 'Excellent' or 'Good,' and ineffective if the intraoperative hemostasis category is 'Moderate' or 'Poor.' A participant will be deemed non-evaluable if s/he meets the criteria specified in the EAC Charter (see Section 5.3.2).

5.3.2. Main Analytical Approach

The number of participants achieving effective hemostasis will be tabulated. An exact Clopper-Pearson 95% CI for the proportion of participants with effective hemostasis will be provided.

All participants in the Efficacy Set will be included in the primary analysis except for certain EAC adjudicated cases as described below.

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 classified by the EAC as 'non-evaluable due to administrative reasons' (eg, participant transferred to another facility for administrative purposes) or 'non-evaluable due to clinical reasons' (eg, participant died).

Participants whose hemostatic efficacy is 'non-evaluable due to administrative reasons' will be excluded in all applicable efficacy analyses.

Participants whose hemostatic efficacy is 'non-evaluable due to clinical reasons' will be considered as having moderate/poor hemostatic efficacy and included in the denominator in the primary analysis as having ineffective hemostasis; but treated as not having an effective hemostasis value and thus excluded in the denominator in a sensitivity analysis (Section 5.3.3).

5.3.3. Sensitivity Analysis

To evaluate the sensitivity of the primary efficacy analysis, the primary efficacy analysis will be repeated with the following changes separately:

- Exclude the hemostatic efficacy values deemed 'non-evaluable due to clinical reasons' by the EAC (which are otherwise automatically included as ineffective hemostasis values in the primary efficacy analysis in Section 5.3.2)
- Include only participants in the Per Protocol Set

5.4. Secondary Endpoint Analysis

The secondary endpoint analysis will be performed on the Efficacy Set unless stated otherwise.

5.4.1. Endpoint

Anti-fXa activity will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Anti-fXa activity will be measured by a modified chromogenic assay. These assays will be performed at a central laboratory.

The secondary efficacy endpoint is the percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts from the end of the andexanet bolus and ends at the end of the andexanet infusion. The baseline measurement will be the last value obtained prior to andexanet treatment. Anti-fXa activity will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Anti-fXa activity will be measured by a modified chromogenic assay. These assays will be performed at a central laboratory.

5.4.2. Main Analytical Approach

The secondary endpoint will be assessed with a 2-sided 95% non-parametric CI for the median. Percent change will be calculated as 100% × (change from baseline to nadir/baseline). Patients who do not have at least 1 anti-fXa activity level within the evaluation period will have percent decrease imputed as 0.0% (i.e., using the baseline value as the nadir value).

5.4.3. Sensitivity Analysis

The same analysis described in Section 5.4.2 will be repeated using the Per Protocol Set.

5.5. Exploratory Endpoint Analysis

All exploratory endpoint analyses will be performed on the Efficacy Set.

The following efficacy endpoints will be analyzed as exploratory:

- Relationship between intraoperative hemostasis and anti-fXa activity
- Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, number of participants with percent reduction from baseline > 80%

- Reversal of anticoagulant effect as measured by thrombin generation (TG) parameters (with endogenous thrombin potential [ETP] as the primary measure)
- Occurrence of receiving 1 or more red blood cell (RBC) transfusions from start of the andexanet bolus through 12 hours after the end of surgery
- The number of RBC units transfused per participant from the start of the andexanet bolus through 12 hours after the end of surgery
- The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery
- Observed amount of intraoperative blood loss
- Difference between observed blood loss and predicted blood loss
- Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery
- Time from the signing of informed consent to the start of surgery
- Time from clinical presentation at treatment facility to the start of surgery
- Length of index hospitalization, assessed at the Day 30 Visit
- Time hospitalized in a post-anesthesia care unit (PACU), assessed at the Day 30 Visit
- Time hospitalized in an intensive care unit (ICU), assessed at the Day 30 Visit
- Length of surgery
- Total time in the operating room (OR)
- Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post enrollment)
- Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria (see Protocol Section 4.1), within 12 hours after the start of the initial surgery
- Occurrence of re-operations for bleeding, including for surgical wound hematomas, within 12 hours after the end of the initial surgery
- Change from baseline in tissue factor pathway inhibitor (TFPI) activity post-administration of andexanet
- Change from baseline in anti-IIa activity (only participants taking enoxaparin)

5.5.1. Relationship Between Anti-fXa Activity and Hemostasis

Anti-fXa activity (percent change from baseline to on-treatment nadir) will be summarized by achievement of hemostatic efficacy (effective versus ineffective).

5.5.2. Anti-fXa Activity – Absolute and Percent Change from Baseline

Absolute change (including on-treatment nadir) and percent change from baseline at each time point will be summarized by FXa inhibitor (apixaban, rivaroxaban, edoxaban [ng/mL];

enoxaparin [IU/mL]). Furthermore, 95% CIs for the mean (absolute change) and the median (percent change) will be provided. On-treatment nadir is the minimum anti-fXa activity from the end of andexanet bolus to the end of the andexanet infusion.

In addition, the number and percent of participants with percent reduction from baseline at any time point > 80% will be tabulated and 95% CI for the proportion will be presented.

5.5.3. Reversal of Anticoagulant Effect - Thrombin Generation

Five parameters related to TG are measured: endogenous thrombin potential (ETP [nM*min]), peak height (nmol), time to peak height (min), lag time (min), and velocity index (nmol/min). ETP is prospectively identified as the primary measure for TG.

For each of the 5 parameters, descriptive statistics and CIs will be provided for baseline and change from baseline values at each applicable time point/visit (Section 6.7).

5.5.4. Blood Product Usage

Blood product usage will be summarized for the following:

- Number of participants receiving 1 or more RBC transfusions from start of the andexanet bolus through 12 hours after the end of surgery
- Mean number of RBC units (treated as a continuous variable) transfused per participant from the start of the andexanet bolus through 12 hours after the end of surgery
- Number of participants receiving non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery

For each of these blood product usage variables, descriptive statistics and CIs will be provided.

5.5.5. Intraoperative Blood Loss

The volume of blood loss (mL) – predicted, actual, and actual minus predicted – will be summarized with descriptive statistics and CIs.

5.5.6. Transfusion-Corrected Change in Hemoglobin

Baseline and change from baseline to nadir (within 12 hours after the end of surgery) in transfusion-corrected (ie, on only those participants having received whole blood or packed RBCs during surgery) hemoglobin (mg/dL) will be summarized with descriptive statistics and CIs.

5.5.7. Healthcare Encounter and Surgical Intervention

Healthcare encounter will be summarized for the following:

- Time from signing of informed consent to start of surgery (hours)
- Time from clinical presentation to start of surgery (hours)
- Duration of index hospitalization (hours)

- Time hospitalized in a PACU (hours)
- Time hospitalized in an ICU (hours)
- Length of surgery (hours)
- Total time in OR (hours)
- Occurrence of re-hospitalization within 30 days of enrollment (yes/no)
- Length of re-hospitalization (days) through 30 days post enrollment, as the aggregate number of days spent re-hospitalized

For each of these healthcare encounter variables, descriptive statistics and CIs will be provided.

5.5.8. Post-Surgical Major Bleeding

Post-surgical major bleeding will be summarized for the following:

- Occurrence of post-surgical bleeding (yes/no), as defined by ISTH criteria (Schulman, 2010; Section 7) within 12 hours after the start of the initial surgery
- Occurrence (yes/no) of re-operations for bleeding (including for surgical wound hematomas) within 12 hours after the end of the initial surgery

For each of these post-surgical major bleeding events, descriptive statistics and CIs will be provided.

5.5.9. Tissue Factor Pathway Inhibitor (TFPI)

The TFPI activity will be measured using plasma samples in a Central Laboratory using a validated assay. The TFPI functional activity will be determined using a commercial kit. The assay measures FXa chromogenic activity following FX activation by factor VIIa/TF added to the plasma. The TFPI activity is quantified by using a TFPI standard with U/mL as the readout. Binding of andexanet to TFPI will reduce the TFPI activity readout.

Baseline and change from baseline in TFPI activity (U/mL) post administration of andexanet will be summarized with descriptive statistics and CIs at each applicable time point/visit.

5.5.10. Anti-IIa Activity

Anti-IIa activity levels will be measured in patients taking enoxaparin using plasma samples. Anti-IIa activity will be measured using a modified chromogenic assay. Anti-IIa activity results will be performed in a Central Laboratory.

Baseline and change from baseline in anti-IIa activity (IU/mL) will be summarized, for participants on enoxaparin only, with descriptive statistics and CIs at each applicable time point/visit.

5.6. Safety Analyses

Safety will be assessed by examining the following endpoints and analyzed using the Safety Set:

- Adverse events (AEs) (including serious adverse events [SAEs]), vital signs, and clinical laboratory measurements

- TEs within 30 days of enrollment, including those suspected and confirmed by adjudication
- Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality
- Antibodies to FX, FXa, and andexanet

5.6.1. Extent of Exposure

Participant compliance with the assigned treatment will not be evaluated since all procedures are performed in the hospital by trained professionals. Treatment modification with corresponding modification type will be tabulated along with descriptive statistics on the length of bolus and infusion duration; these results will be summarized by the dose of andexanet received (low, high, Total). Results will be presented for overall and by prior FXa inhibitor for the Safety Set.

5.6.2. Adverse Events

Adverse events are defined in Protocol Section 9.1.1 and Section 6.1 of this statistical analysis plan.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 23.0 or later. In the analysis of treatment-emergent adverse events (TEAEs), all events recorded as occurring before first study treatment will be considered baseline conditions. Related TEAEs are events considered related to study treatment by the Investigator.

The number of events and the number of participants who experienced at least one 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 medication or usual care, TEAEs that lead to early withdrawals, and SAEs will be summarized in the same manner.

5.6.2.1. Overall Summary of Adverse Events

An overall summary of TEAEs and SAEs will be presented. The number of events (E) and number of participants with events (n, %) will be shown for the following:

Table 3: Treatment-Emergent Adverse Events (TEAEs) and Serious AEs

Events
Any Adverse Event
Adverse Events Leading to Withdrawal of Study Drug
Adverse Events by Relationship (Related, Not Related)
Adverse Events by Severity (Mild, Moderate, Severe)
Adverse Events of Special Interest (Arterial Systemic Embolism, Deep Vein Thrombosis, Myocardial Infarction, Pulmonary Embolism, Ischemic Stroke, Transient Ischemic Attack)

These tabulations will be prepared separately for all TEAEs and SAEs. Additionally, the number and percentage of participants who died on study will be presented.

5.6.2.2. TEAEs and SAEs by System Organ Class (SOC) and Preferred Term

The number and percentage of TEAEs will be presented by SOC and Preferred Term. At the participant level, participants are counted once in each SOC and Preferred Term. Percentages

will be based on the total number of treated participants. SOCs will be listed in alphabetical order, and Preferred Terms within each SOC will be sorted by descending frequency of participants reporting the event.

SAEs, TEAEs leading to withdrawal of study drug, and TEAEs occurring in ≥5% of patients will be tabulated by SOC and Preferred Terms in a similar manner.

Additional tables summarizing TEAEs by surgery type and baseline FXa inhibitor may also be provided.

TEAEs and treatment-emergent related adverse events will also be tabulated but at the Preferred Term level only, for number of participants as well as for number of events, with Preferred Terms sorted by descending frequency.

Participants with events during the screening period (Pre-treatment adverse events [PTAEs]) will be presented in a data listing.

5.6.2.3. AEs and SAEs by SOC, Preferred Term, and Relationship

The number of TEAEs and the number and percentage of participants with events will be presented by SOC and Preferred Terms for all relationship levels (related, not related); if a participant has multiple events at the same relationship status for a particular SOC or Preferred Term, he/she is counted only once for that SOC or Preferred Term but all occurrences are counted at the event level. SAEs will be summarized similarly.

5.6.2.4. AEs and SAEs by SOC, Preferred Term, and Severity

The number and percentage of participants with events will be presented by SOC and Preferred Term as described above, by worst severity (mild, moderate, severe). If a participant has more than one occurrence of a TEAE, the most severe occurrence will be summarized for each participant per SOC/Preferred Term.

5.6.2.5. Deaths, Other SAEs, and Other Significant Adverse Events

The number and percentage of participants with adverse events leading to death will be presented by SOC and Preferred Term as described above. Additionally, those events leading to death which were COVID-19 related will also be tabulated in a similar fashion.

Furthermore, participants will have their survival status reported by phone on the Day 30 or End of Study visit. This assessment will record the participant's status as alive or provide the date, time, and cause of death. All deaths will be assessed by the EAC. Deaths will be classified by the following:

- Cardiovascular causes (ie, resulting from myocardial infarction [MI], sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, and other cardiovascular causes)
- Non-cardiovascular causes

All participants who died up through the 30-Day Follow-up Visit will be tabulated by reason for death (Cardiovascular, non-cardiovascular). In addition, 95% CIs for the proportions will be reported.

5.6.2.6. Adverse Events of Special Interest (AESIs)

Participants will be monitored carefully for signs and symptoms of TEs (version 23.0 or later computed tomography [CT]/magnetic resonance imaging [MRI], electrocardiogram [ECG]/cardiac enzymes, lower extremity ultrasound, pulmonary vascular imaging). Investigators are requested to consult the guidance listed in the protocol when considering whether an event should be considered a TE and therefore, be submitted for adjudication. All events submitted for adjudication will be formally considered a suspected TE. Both suspected TEs and TEs confirmed by adjudication will be monitored as safety endpoints.

All TEs up to the last study visit (ie, Day 30) will be assessed by the EAC and summarized descriptively, including whether (and to what extent) participants were re-anticoagulated prior to the thrombotic event up to the last study visit (ie, Day 30).

The Investigator will determine whether a TE is attributable to andexanet, while the DSMB will determine whether the occurrence of TEs in aggregate (related or not) warrant changes to the study. Detailed definitions of thrombotic events (including arterial systemic embolism, deep vein thrombosis, myocardial infarction, pulmonary embolism, ischemic stroke, and transient ischemic attack) will be provided in the EAC Charter as well as in the protocol.

The following tabulation of TEs will be performed:

- Incidence of suspected TEs, by detailed adverse event of special interest (AESI) term (arterial systemic embolisms, cerebrovascular accident or stroke, deep vein thromboses, myocardial infarction, pulmonary embolisms, transient ischemic attacks)
- Incidence of TEs confirmed by adjudication, by detailed AESI term (arterial systemic embolisms, cerebrovascular accident or stroke, deep vein thromboses, myocardial infarction, pulmonary embolisms, transient ischemic attacks)

5.6.3. Analyses for Laboratory Tests

In general, only laboratory value collected at scheduled visit/time points will be summarized. Laboratory value collected at unscheduled visits will be presented in data listings only. If an assessment is repeated for a given scheduled visit/time point, the last value will be used for summary purposes, but all values will be presented in data listings.

5.6.3.1. Hematology

Hematology (hemoglobin, hematocrit, white blood cell [WBC] count, platelet count, WBC differential) assays are performed at the local laboratory and will be summarized using standardized units.

Descriptive statistics will be provided for the values at each time point as well as change from baseline at each time point. Tabulations will be performed for abnormal values relative to normal ranges at each visit, as well as shifts from baseline (low, normal, high) to each applicable time point/visit.

WBC differentials may be collected as absolute values and/or percentages. While only absolute values will be summarized, both absolute values and percentages will be presented in data listings. In cases where only the differential percentage is collected per local laboratory standards, the absolute value of the WBC type (eg, neutrophils) will be imputed for analysis as:

WBC type absolute value = WBC absolute count * WBC type differential percentage

5.6.3.2. Coagulation

Prothrombin time (expressed as INR) is collected at Screening only. Descriptive statistics will be presented for INR.

5.6.3.3. Serum Chemistry

Serum chemistry (sodium, potassium, chloride, carbon dioxide [bicarbonate], glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin) assays are performed at the local laboratory and will be summarized using standardized units.

Serum chemistry parameters are collected at Screening only. Descriptive statistics by time of assessment will be presented for each chemistry parameter. All chemistry values will be classified as normal, below normal, or above normal based on normal ranges supplied by the local laboratory. Frequencies of abnormal values will be presented in tabular form.

5.6.3.4. Pregnancy Test

Serum or urine pregnancy tests for women of childbearing potential are administered at Screening. Pregnancy test results (positive/negative) will be provided in a data listing.

5.6.3.5. Optional Local Laboratory Testing of Anti-fXa Levels

Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion criteria. These results will be provided in a data listing only.

5.6.3.6. Antibodies

Determination of the possible presence of antibodies to FX (human) and FXa (human) will be made at Screening and on the Day 30 or End of Study Visit using the modified Bethesda assay. Antibodies against andexanet will be assessed using standard immunogenicity assays.

For any sample that is positive for antibodies against andexanet, the potential for neutralizing antibody (NAb) activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a central laboratory.

The presence of antibodies (anti-andexanet, anti-fX, anti-fXa, and/or NAb activity) will be presented in a listing.

5.6.4. Vital Signs and Weight

Vital signs include temperature (°C), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), heart rate (beats per minute), and respiratory rate (respirations per minute), are collected at various time points before and after the surgical procedure. Reported weight (kg) and actual weight (kg) are collected on the vital signs case report form (CRF) at the Screening and Day 30/ET Visit, respectively.

Vital signs will be summarized using actual values and change from baseline at pre-specified time points. Additionally, the number of participants having clinically significant vital signs at each visit will be tabulated using the following criteria:

- Temperature: Increase of ≥ 1.1°C or ≥ 38.3°C
- Heart Rate, ≥18 years: (≤ 50 bpm or ≥ 110 bpm) and (decrease of ≥ 15 bpm from baseline or increase of ≥ 15 bpm from baseline)
- Systolic Blood Pressure, ≥ 18 years: (≤ 90 mmHg or ≥ 150 mmHg) and (decrease of ≥ 20 mmHg from baseline or increase of ≥ 20 bpm from baseline)
- Diastolic Blood Pressure, ≥ 18 years: (≤ 50 mmHg or ≥100 mmHg) and (decrease of ≥ 15 mmHg from baseline or increase of ≥ 15 bpm from baseline)

A by-participant listing of vital signs will be provided.

Weight at the Screening and Day 30/ET Visits will be presented in the data listings only.

5.7. Other Analyses

5.7.1. Concomitant Bleeding-Related Diagnostic and Therapeutic Procedures

A participant listing will be presented for all concomitant bleed-related diagnostic and therapeutic procedures captured in the CRFs.

5.7.2. Subgroup Analyses

Consistency of efficacy across important subgroups will be investigated within each cohort. The primary efficacy endpoint will be summarized for the following subgroups:

- age (< 65 years, ≥ 65 years)
- sex (male, female)
- race (all CRF pre-specified groups with 5 or more participants; “Other” and groups with fewer than 5 participants will be combined)
- FXa inhibitor (apixaban, edoxaban, rivaroxaban, enoxaparin)
- procedure type (orthopedic, abdominal, thoracic, neurosurgical, other)
- duration of surgery (< 2 hours, 2 to 4 hours, > 4 hours)
- volume (mL) of observed blood loss (< median, ≥ median)

Summarization for each subgroup will be identical to that for the primary efficacy analysis (Section 5.3.2).

5.8. Interim Analyses

No interim efficacy analyses are planned for this Phase 2 study, however, an independent DSMB will review study data once the 30-Day Visit is completed for the participant recruitment of approximately 33 and 66 participants. DSMB analyses will be described in a separate DSMB analysis plan.

5.8.1. EAC and DSMB

Each of planned study committees will have a charter outlining its activities and responsibilities. In brief, the purpose of each committee is as follows:

- Independent EAC: Adjudication of hemostatic efficacy, deaths, TEs, and post-surgical bleeding events for all participants. The EAC will be blinded to all anti-fXa levels.
- Independent DSMB: Monitor all safety data and make recommendations for study modification or stopping due to safety reasons.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Hospital Length of Stay

Hospital length of stay (LOS): Duration of the index hospitalization. The following steps will be followed to calculate the LOS (days):

- The LOS will be calculated as the number of days (discharge date minus the admission date) plus 1
- If participant admission time and the discharge time is missing and the dates are the same, the LOS will be assumed to be 1 day
- If participant admission time and the discharge time is 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 earliest) will be imputed as the discharge date. The imputed date will be used for the LOS and in-hospital mortality
- If a 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 earliest)

Calculation of On Treatment Nadir

On treatment nadir is the minimum anti-fXa activity from the end of bolus to the end of andexanet infusion. Percent change will be calculated as (100% × [on treatment nadir – baseline] / baseline).

Interquartile Range (IQR)

IQR calculated as 75th percentile – 25th percentile.

Definition of Baseline Values

Anti-fXa Activity: Baseline is the last value obtained prior to andexanet treatment.

General: Baseline is the last value obtained prior to andexanet treatment.

Change from Baseline

Change from baseline will be calculated as the post-baseline value minus the baseline value.

Percent Change from Baseline

Percent change from baseline will be calculated as 100% × (change from baseline/baseline).

Adverse Events

The analysis of AEs is described in detail in Section 5.6.2.

AE reporting period starts with signing of the informed consent form (ICF) and continues through the Day 30 Follow-up Visit.

Treatment-emergent AEs (TEAEs) are new adverse events with start dates and start times on or after the date and time of the first study treatment dose, or PTAEs that have worsened in severity since the date and time of the first study treatment dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose of study treatment, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study treatment dose, then the AE is treatment emergent; else,
- If the start year is the same as the year of the first study treatment dose and
  - the start month is missing, then the AE is treatment emergent; else if
  - the start month is present and is the same or after the month of the first study treatment dose, then the AE is treatment emergent; else,
- If the start date is completely missing, then the AE is treatment emergent.

All other AEs are considered PTAEs.

Related AEs are defined as unrelated or related. Unrelated AEs are defined as unlikely or unrelated. Events with missing relationship are defined as related.

Concomitant Medications

Concomitant medications are medications with start dates and start times on or after the date and time of the first study treatment dose (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. For further information and definition of prior medications see Section 6.2.4.

6.2. Appendix 2: Study and Participant Characteristics

6.2.1. Protocol Deviations

Protocol deviations will be tabulated for the Safety and Efficacy Sets and will be presented for overall and for major deviations.

Deviations categories will include the following:

- Eligibility and Entry Criteria
- Investigational Product Compliance
- Concomitant Medication Criteria
- Informed Consent Criteria
- Laboratory Assessment Criteria

- Visit Schedule Criteria
- Study Procedures Criteria
- Serious Adverse Event Criteria
- Source Document Criteria
- Other Criteria

Major deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect participant's rights, safety, or well-being. Major deviation criteria will be determined prior to database lock.

Details around protocol deviations specific to the primary efficacy endpoints are provided as follows:

- Protocol deviations related to the evaluation of hemostatic efficacy will be considered significant (major) if the adjudication decision is impacted by the deviation
- The majority of protocol deviations regarding the hemostatic efficacy endpoints will be considered by the EAC. Any protocol deviations not considered by the EAC may be individually considered within the analysis of the data and discussed in the Clinical Study Report (CSR)

6.2.2. Demographics, Baseline Characteristics, and History

Baseline and demographic characteristics will be summarized for the Safety and Efficacy Sets. Urgent surgery characteristics, medical/surgical history, and prior/concomitant medications, and COVID-19 diagnosis will be summarized for the Safety Set.

6.2.2.1. Demographics

The following demographic parameters will be summarized:

- Sex (Male, Female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Unknown)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Age (years): descriptive statistics
- FXa inhibitor (apixaban, rivaroxaban, enoxaparin, edoxaban)
- Baseline anti-fXa activity:
  - apixaban, rivaroxaban, edoxaban: a) < 30 ng/mL, b) between ≥ 30 ng/mL and <75 ng/mL, c) ≥ 75 ng/mL
  - enoxaparin: a) < 0.5 IU/mL, b) ≥ 0.5 IU/mL

6.2.2.2. Urgent Surgery Characteristics

The following characteristics related to the urgent surgical event will be summarized. These summaries will be done for both the Safety and Efficacy Sets:

- Participant presentation location (clinic, transfer from outside hospital, hospitalization, emergency department (ED) stay, PACU, ICU stay, other)
- Type of surgical intervention
- Time from hospitalization to study treatment (hours)
- Time from last FXa inhibitor dose to start of surgery (hours)
- Surgery duration (hours)

6.2.3. Medical / Surgical History and Baseline Physical Examination

Medical history will be coded using MedDRA version 23.0 or later. The number of participants with any medical history will be tabulated. The number of participants with at least 1 medical history will also be tabulated by SOC and Preferred Term; if participants experienced more than 1 history in a specific SOC or Preferred Term, they will be counted only once for the SOC or Preferred Term.

6.2.4. Prior and Concomitant Medications

All medications used following informed consent through End of Study (Day 30) will be tabulated and coded using the World Health Organization Drug Dictionary (WHODrug) version September 2020 or later. Prior medications that are ongoing at the time of first study treatment will be tabulated separately from concomitant medications. Summaries of participants using prior and concomitant medications will be presented by WHODrug Anatomical Therapeutic Chemical (ATC) Level 3 and by WHODrug generic name.

Medications will be classified based on all available date and time information. Prior medications are those taken before or at the time of study treatment. For any medication, unless there is clear evidence suggesting it started after the time of first dose of study treatment, it will be classified as a prior medication. Concomitant medications are those taken at or after the time of study treatment. For any medication, unless there is clear evidence suggesting it ended before the time of first dose of study treatment, it will be classified as a concomitant medication. If the available information is insufficient for unequivocal classification, the medication will be classified as both a prior medication and a concomitant medication for summarization.

6.2.5. COVID-19 Impact

The number of participants with any number of visits missed or modified due to exposure to, or diagnosis of COVID-19 will be tabulated. A listing of these participants along with the COVID-19 related reason(s) for visit modification, or primary reason for missed visit will be provided for each visit impacted by COVID-19.

6.2.6. American Society of Anesthesiologists Physical Status Classification

The American Society of Anesthesiologist Physical Status Classification (ASA PS) is used to evaluate and describe the general health of participants prior to use of anesthetics or prior to surgery. The ASA PS consists of 6 categories to describe a participant's physical status (Protocol Appendix F). It will be used to describe the population enrolled in the study. It is not an assessment of operative risk and will not be repeated during the study. ASA PS categories will be tabulated.

6.3. Appendix 3: Instrument Scoring Details

Not applicable.

6.4. Appendix 4: Additional details on Statistical Methods

Guidance SAS code will be provided in a separate data presentation plan (DPP).

6.5. Appendix 5: Changes to Protocol-planned Analyses

6.5.1. Changes from Protocol to SAP V1.0

1. Protocol Section 11.3: Three analysis populations were defined: Enrolled, Safety Analysis, and Efficacy Analysis. A fourth analysis population, the "Per Protocol Set", was defined in this statistical analysis plan to provide additional robustness to the primary and secondary efficacy analyses that are based on the Efficacy Set.
2. Protocol Section 11.3: The baseline anti-fXa activity evaluability threshold for edoxaban participants to be included in the Efficacy Set has been changed from 75 ng/mL to 40 ng/mL to match updated study entry criterion.
3. Protocol Sections 11.5.X: The definition of the evaluation period for anti-fXa activity has been changed from "5 minutes following the end of the andexanet bolus to just prior to the end of the andexanet infusion" in the protocol to "the end of the andexanet bolus to the end of the andexanet infusion" in this SAP. This change reflects more appropriately the time window during which post-treatment anti-fXa activity is intended to be evaluated.
4. Protocol Section 11.5.1: Hemostatic efficacy will be assessed by the investigator, instead of by the surgeon as stated in the protocol, per an administrative change letter distributed to the study sites post approval of Protocol Amendment #2.
5. Protocol Section 11.5.2.3: Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and hemostasis (ISTH) criteria, should be assessed within 12 hours after "the start of the initial surgery", instead of "the end of the initial surgery" as stated in the protocol due to a typo per an administrative change letter distributed to the study sites post approval of Protocol Amendment #2.
6. Protocol Section 11.7: Antibodies to host-cell proteins (HCPs) will not be considered a safety endpoint as they are no longer planned to be collected.
7. Protocol Section 11.7.6: Physical examination will be conducted but results are not explicitly collected in the case report forms (CRFs). Consequently, no physical examination results will be presented. However, clinically significant findings will be recorded on the adverse event CRFs and reported as such.
8. Protocol Section 11.9: Subgroup analysis of effective hemostasis based on age categories has been changed from (< 65 years, ≥ 65 years, and ≥ 75 years) to (< 65 years and ≥ 65 years) to eliminate category overlap and for symmetry.
9. Protocol Section 11.9: Subgroup analysis of effective hemostasis based on anticoagulant indication has been removed since anticoagulant indication is not considered to be an important factor.

10. Protocol Section 11.9: Subgroup analysis of effective hemostasis based on volume (mL) of observed blood loss has been changed from (above and below the median) to (< median, ≥ median) to ensure values exactly at the median will be included.

6.6. Appendix 6: List of Abbreviations

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 4: List of Abbreviations and Acronyms

Abbreviation or Acronym	Definition/Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
Andexanet alfa	Recombinant factor Xa inhibitor antidote
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
ED	Emergency Department
ET	Early Termination
ETP	Endogenous Thrombin Potential
fX	Factor X
fXa	Factor Xa
HCP	Host Cell Protein
HR	Heart Rate
ICF	Informed Consent Form
ICU	Intensive Care Unit
INR	International Normalized Ratio
IQR	Interquartile Range
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
LOS	Length of Stay
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
NAb	Neutralizing Antibody
OR	Operating Room
PACU	Post-Anesthesia Care Unit
PPS	Per Protocol Set
PT	Preferred Term
PTAE	Pre-Treatment Adverse Event
RBC	Red Blood Cells
RR	Respiratory Rate
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class
SS	Safety Set
TE	Thrombotic Event
TEAE	Treatment-Emergent Adverse Event

TFPI	Tissue Factor Pathway Inhibitor
TG	Thrombin Generation
WBC	White Blood Count
WHODrug Dictionary	World Health Organization Drug Dictionary

6.7. Appendix 7: Protocol Schedule of Events

	Screening & Baseline		**Treatment**						**Follow-up**		
STUDY DAY:	**1**								**2**	**3**	**30 or ET**
				SURGERY			**Post-Surgery**				
			Bolus/Infusion Administration (can start up to 30 min before SoS)								
TIME POINT AND WINDOW:	**-2 hours to -45 min Relative to SoS**	**-45 min to -30 min Relative to SoS**	**-30 min to -5 min Relative to SoS**	**End of Bolus** ± 15 min	**EoII** -15 min	**EoS [1]** + 15 min [2]	**EoS + 6 h** ± 1 h	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 48 h** ± 1 h	+ 7 days
Obtain Consent	X										
Determine Eligibility	X										
Obtain Medical History	X										
Demographics	X										
Obtain Prior Medications and Time of Last Anticoagulant Dose or Plasma Level	X										
Obtain ASA Class			X								
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X		X	X	X	X
Weight (actual reported/recent)	X										X
Physical Examination	X							X	X	X	X
Central Labs: Anti-fXa and anti-IIa Activity		X (pre-ADX)		X	X	X	X	X			
Central Labs: Thrombin Generation		X (pre-ADX)		X	X	X	X	X	X	X	
Central Labs: Antibodies to andexanet, HCPs, and FX/FXa (modified Bethesda); and NAb (andexanet)	X (pre-ADX)										X

	Screening & Baseline		**Treatment**						**Follow-up**		
STUDY DAY:	**1**								**2**	**3**	**30 or ET**
				SURGERY			**Post-Surgery**				
			Bolus/Infusion Administration (can start up to 30 min before SoS)								
TIME POINT AND WINDOW:	**-2 hours to -45 min Relative to SoS**	**-45 min to -30 min Relative to SoS**	**-30 min to -5 min Relative to SoS**	**End of Bolus** ± 15 min	**EoII** -15 min	**EoS [1]** + 15 min [2]	**EoS + 6 h** ± 1 h	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 48 h** ± 1 h	+ 7 days
Central Labs: TFPI activity		X (pre-ADX)		X	X	X		X	X	X	X
Local Labs: PT-INR	X										
Local Labs: Chemistry and Pregnancy Test [3]	X										
Local Labs: CBC		X				X		X			X
Prepare Andexanet	X										
Administer Andexanet Bolus, Immediately Followed by an Infusion			**X**								
Assess Need for Extended Andexanet Infusion (if surgery ongoing)					X [4]						
Estimate Predicted Blood Loss			**X [5]**								
Surgical Intervention				**SURGERY**							
Record Blood Loss Post Surgery						X					
Record Investigator Assessment of Intraoperative Hemostasis						X					
Record Blood Products & Hemostatic Treatments [6]		X									

	Screening & Baseline		**Treatment**						**Follow-up**		
STUDY DAY:	**1**								**2**	**3**	**30 or ET**
				SURGERY			**Post-Surgery**				
			Bolus/Infusion Administration (can start up to 30 min before SoS)								
TIME POINT AND WINDOW:	**-2 hours to -45 min Relative to SoS**	**-45 min to -30 min Relative to SoS**	**-30 min to -5 min Relative to SoS**	**End of Bolus** ± 15 min	**EoII** -15 min	**EoS [1]** + 15 min [2]	**EoS + 6 h** ± 1 h	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 48 h** ± 1 h	+ 7 days
Record Bleeding-Related Diagnostic & Therapeutic Procedures [7]		X							X	X	
Record Volume of Colloid and Crystalloid [6]		X									
Record Hours in ED, PACU, ICU/Critical Care, General Hospital Floor, and Total as an Inpatient											X
Record AEs and any TEs	X	X							X	X	X
Record Concomitant Medications	X	X							X	X	X
Ascertain Survival Status											X

	Re-Dose of Andexanet		
STUDY DAY:	**1**		
TIME POINT AND WINDOW:	**Pre-Start of Bolus** -15 min	**End of Bolus** +15 min	**Pre-End of Infusion** -15 min
Initiate Andexanet Low Dose Bolus + Infusion	X		
Central Labs: Anti-fXa and anti-IIa Activity	X (pre-ADX)	X	X

[1] The EoS time point may occur before the EoII; EoS procedures should be carried out when EoS occurs.
[2] Collect EoS samples within 15 minutes from the end of surgery but before stopping infusion.
[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.
[4] Approximately 30 to 45 minutes prior to the end of the andexanet infusion, the Investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.
[5] Prior to the first incision, predicted blood loss must be determined by the Investigator.
[6] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.
[7] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.
ADX = andexanet; AE = adverse event; ASA = American Society of Anesthesiologists; BP = blood pressure; CBC = complete blood count; ED = emergency department; EoII = end of initial infusion; EoS = end of surgery; ET = early termination; FX = factor X; FXa = activated factor X; h = hour(s); HCP = host-cell protein; HR = heart rate; ICU = intensive care unit; INR = international normalized ratio; min = minute(s); NAb = neutralizing antibody (activity); OR = operating room; PACU = post-anesthesia care unit; PT = prothrombin time; RR = respiratory rate; SoS = start of surgery; TE = thrombotic event; Temp = temperature; TFPI = tissue factor pathway inhibitor

7. REFERENCES

Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost. 2010; 8(1): 202-204.