Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding (ANNEXA-4)

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STATISTICAL ANALYSIS PLAN

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO HAVE ACUTE MAJOR BLEEDING (ANNEXA-4)

Protocol Reference: 14-505

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APPROVAL

Product: Andexanet Alfa

Protocol Number: 14-505

Version: 4.1

Version Date: 30-JUNE-2020

The undersigned have reviewed this Statistical Analysis Plan and find it to be consistent with the protocol as it applies to their respective areas.

Approver	Signature	Date
PPD Portola Pharmaceuticals, Inc.	PPD	30 Jun 2020 9:27 AM
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PPD Portola Pharmaceuticals, Inc.		
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TABLE OF CONTENTS

List of Tables

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event
Andexanet alfa	Recombinant factor Xa inhibitor antidote
AESI	Adverse Event of Special Interest
ASE	Arterial Systemic Embolism
AUC	Area Under the Curve
CI	Confidence Interval
CP	Completers Population
CT	Computed Tomography
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
EAC	Endpoint Adjudication Committee
EOB	End of Bolus
EOI	End of Infusion
ETP	Endogenous Thrombin Potential
FFP	Fresh Frozen Plasma
FX	Factor X
FXa	Factor Xa
GCS	Glasgow Coma Score
HCP	Host Cell Protein
ICH	Intracranial Hemorrhage
ITT	Intent-to-Treat
JTC	Jump to Control
LOS	Length of Stay
MAR	Missing at Random
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
NIHSS	National Institutes of Health Stroke Scale
PCC	Prothrombin Complex Concentrate
PE	Pulmonary Embolism

Abbreviation	Definition
PP	Per Protocol
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
TE	Thrombotic Event
TEAE	Treatment-Emergent Adverse Event
TIA	Transient Ischemic Attack

1.0 INTRODUCTION

This document details the statistical analyses that will be performed for Portola Pharmaceuticals, Inc. (Portola) Study 14-505 "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding (ANNEXA-4)". This Statistical Analysis Plan (SAP) is based on ANNEXA-4 Protocol Amendment 6, dated 30 November 2018. Documents related to this SAP are:

- Andexanet alfa (ANNEXA-4) Study 14-505 Protocol Amendment 6, titled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding (ANNEXA-4)."
- Data Safety Monitoring Board (DSMB) Charter, Version 2.0, dated 20 October 2015.
- ANNEXA-4/Usual Care Cohort Endpoint Adjudication Committee Charter, Final Version 5.0, dated January 30, 2018.

To support marketing authorization submissions for the Food and Drug Administration (FDA) and European Medicines Agency (EMA), analysis will be performed on all N=477 locked patients in the database.

2.0 STUDY OBJECTIVES

The objectives of the ANNEXA-4 study, as stated in Protocol Amendment 6, are as follows:

2.1. Primary Efficacy Objectives

- To demonstrate the decrease in anti-factor Xa (FXa) activity following andexanet treatment.
- To evaluate the hemostatic efficacy following andexanet treatment.

2.2. Secondary Efficacy Objective

- To assess the relationship between decrease in anti-fXa activity and achievement of hemostatic efficacy in patients receiving FXa inhibitor who have acute major bleeding and reduced FXa activity.

2.3. Exploratory Efficacy Objectives

- For patients receiving apixaban, rivaroxaban, or edoxaban, to evaluate the decrease in the free fraction of the FXa inhibitor following andexanet treatment.
- To evaluate the effect of andexanet on thrombin generation.
- To evaluate the effect of andexanet on levels of tissue factor pathway inhibitor (TFPI).
- To evaluate the effect of andexanet on levels of antithrombin III (ATIII).
- To evaluate the effect of andexanet on anti-factor IIa levels for patients receiving enoxaparin.
- To evaluate hemostatic efficacy in intracranial hemorrhage (ICH) patients at high risk for hematoma expansion.
- To evaluate the use of red blood cell transfusions.
- To evaluate the use of other blood products and hemostatic agents.
- To evaluate the occurrence of adjudicated re-bleeding in patients following andexanet treatment. Re-bleeding is defined as follows: recurrent bleeding from the same or another anatomical site, or new bleeding from a different anatomical site in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. For patients with ICH, to evaluate change in clinical status following andexanet treatment.

2.4. Safety Objectives

- To evaluate the overall safety of andexanet including: treatment-emergent adverse events (TEAEs), adjudicated thrombotic events (TEs) and deaths, vital signs, clinical laboratory measurements, and antibodies to FX, FXa, and andexanet.

- To evaluate the all-cause 30-day mortality.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design

ANNEXA-4 is a Phase 3b/4, open-label, single-arm, prospective, multicenter study of andexanet alfa (referred subsequently as 'andexanet') in patients presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin.

Once consent is obtained and eligibility criteria are confirmed, patients with acute major bleeding received andexanet as an IV bolus administered over approximately 15 to 30 minutes, followed immediately by a continuous infusion administered over approximately 120 minutes. The start of the andexanet bolus must be within 18 hours following the last dose of FXa inhibitor, if the timing of the last dose is known, designed to ensure patients have therapeutic anti-fXa activity levels. If the timing of the last dose of FXa inhibitor is unknown, the andexanet infusion must begin as soon as possible following the signing of the inform consent form (ICF) and completion of pre-treatment procedures, but no later than 3 hours following the signing of the ICF. It is expected that approximately 350 patients will be enrolled so that at least 110 ICH patients (Intracranial Hemorrhage), 50 of whom are deemed to be high risk, are evaluable.

Patients will receive one of two dosing regimens of andexanet (see Protocol Amendment 6, Section 6.2) based on which FXa inhibitor they received and the dose and timing of the most recent dose. Anti-fXa activity will be collected at baseline, end of bolus, end of infusion, and at 4, 8 and 12 post infusion. Hemostatic efficacy will be evaluated using a rating system developed for a pivotal study of anticoagulant reversal [1]. The rating is based upon the collection of objective assessments at baseline and specified time points during the 12 hours post administration of andexanet. Assessments include but are not limited to the following: CT or MRI and clinical metrics (Glasgow Coma Scale (GCS), modified Rankin Score (mRS), National Institutes of Health Stroke Scale (NIHSS) at baseline, 1 hour and 12 hours for ICH, MRI/CT for spinal bleeds (within 12 hours); echocardiogram for pericardial bleed (within 12 hours); and transfusion-corrected hemoglobin and hematocrit for other non-visible bleeding (baseline through 12 hours).

A detailed schedule of events can be found in Protocol Appendix A and a schematic of the first 12 hours of Day 1 can be found in Protocol. Adverse Events will be followed through a Day 30 post-treatment visit (to be conducted no later than 37 days after enrollment).

3.2. Sample Size

The sample size, as conceived in the original protocol, was based on the second primary efficacy variable. A sample size of 162 efficacy evaluable patients would provide 80% power for a two-sided 95% CI that is completely above 50% for the second primary efficacy variable of effective hemostasis, demonstrating a response rate above 50% for that variable. This is based on an anticipated response rate of 61%.

Also, it was estimated that ~30% of the safety population will have anti-fXa activity < 75 ng/mL (0.25 IU/mL for patients receiving enoxaparin) and therefore will not be included in the primary analysis. Additionally, it is estimated that up to 5% of patients will be non-evaluable for reasons unrelated to andexanet. Given these factors, the original sample size of the study was set to 250 patients. With the implementation of Protocol Amendment 4 (per a request from the FDA to enrich the enrolled population with ICH patients), enrollment was to continue until at least 110 evaluable ICH patients were enrolled to more comprehensively capture clinical outcomes in this high risk patient population. Therefore, to accommodate this request, the sample size was increased to a total enrollment of 350 patients.

With the implementation of Protocol Amendment 6, the final sample size was adjusted based on changes in enrollment strategy for various bleed types and FXa inhibitors, a need to meet regulatory requirements for sufficient numbers of patients for each FXa inhibitor and/or geographic region, or new information from registries, observational studies, clinical trials, and/or other sources. To accommodate a potential increase in sample size based on these factors, the overall enrollment was increased to 500 patients.

3.3. Randomization

This is a prospective, open-label study with a single treatment arm. Consequently, there is no randomization.

3.4. Endpoint Adjudication Committee

An independent Endpoint Adjudication Committee (EAC) will convene to adjudicate the following:

- Bleeding entry criteria for inclusion in the Efficacy Population (yes, no).
- Hemostatic efficacy (excellent, good, poor/none, administrative non-evaluable, non-administrative non-evaluable).
- Thrombotic events (yes, no).
- Deaths (cardiovascular, non-cardiovascular).
- Re-bleeding (yes, no).

The EAC will adjudicate all endpoints blinded to the results of the anti-fXa evaluation. Details of the EAC policies and procedures are presented in the Endpoint Adjudication Charter.

3.5. Interim Analysis

Formal interim analyses to evaluate the efficacy of andexanet were not pre-specified. However, periodic safety summaries having a minimum frequency of once a year, including a semi-annual DSMB review and an annual DSUR update (Development Safety Update Report) were performed. In addition, descriptive efficacy and/or safety submissions were provided for regulatory purposes/requests.

4.0 ANALYSIS VARIABLES

4.1. Disposition

4.1.1. Discontinuation from Study

Reasons for discontinuation will be defined as follows:

- Withdrawal of Consent
- Death
- Lost to Follow-up
- Early Withdrawal
- Intolerable TEAE/SAE that cannot be ameliorated by appropriate medical intervention
- TEAE/SAE that in the Investigator's opinion would lead to undue risk
- Other

Time of Discontinuation: Time to discontinuation will be defined as the length of time from start of andexanet treatment to study discontinuation. Time to discontinuation will be expressed as number of hours and in days.

4.1.2. Reason for Exclusion from Efficacy Population

The Efficacy Analysis Population is defined in Section 5.2.2. The reasons for exclusion of patients from Efficacy Population will be categorized as follows:

- Patients with missing baseline anti-fXa level.
- Patients who did not meet the clinical bleeding inclusion criteria.
- Patients with baseline anti-fXa level of less than 75 ng/mL for apixaban and rivaroxaban, 40 ng/mL for edoxaban, or 0.25 IU/mL for patients receiving enoxaparin.
- The patient met neither the bleeding nor the anti-fXa criteria.

4.2. Demographic and Baseline Characteristics

4.2.1. Demographic Variables

- Protocol Version to which subject was enrolled
- Age (years)
- Age Category: < 65, 65 – 75, > 75 years
- Age Deciles: < 19 years; 19 – 29, 30 – 39; 40 -49; 50 – 59, 60 -69, 70 – 79, 80 -89, 90 – 99 years
- Sex (Male, Female)

- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not responded, Unknown)
- Primary Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other). For patients enrolled in Japan with Japanese ancestry, the race should be designated as Japanese.
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Estimated glomerular filtration rate (eGFR): eGFR will be estimated in mL/min using the Cockcroft and Gault equation as follows:
  - If patient is "Female" eGFR = 0.85 * (140- AGE) * WEIGHT / (AVAL * 72)
  - If patient is "Male" eGFR = (140- AGE) * WEIGHT / (AVAL * 72)
  - AVAL = creatinine at baseline, pre-andexanet dosing
- Bleeding Type: Bleeding type will be defined based on the screening evaluation performed by the investigator (i.e., primary bleeding assessment, CRF #208) and on the adjudication. The adjudicated bleeding entry criteria is defined by the EAC as presented in CRF #120. Investigator assessment is defined as follows:
  - GI if primary bleed is GI,
  - ICH if primary bleed is Intracranial Hemorrhage,
  - Other if primary bleed is Urinary, Muscular/skeletal non-visible, other non-visible, or Visible.
  - Multiple primary bleed types should be concatenated and separated by a semi colon.
- Time from Baseline Scan to Andexanet Treatment: Time from baseline scan to start of andexanet is calculated as the difference in hours from time of baseline scan (CRF #160, screening CRF) to the start of andexanet (CRF #010/210, bolus start).
- Time from Bleeding to Andexanet Treatment: Time from bleeding to andexanet treatment is calculated as the difference in hours from the onset of primary bleeding (CRF #008/208) to start of andexanet treatment (CRF #010/210, bolus start).
- Time from Bleeding to Baseline Scan: Time from bleeding to scan is calculated as the difference in hours from onset of primary bleeding (CRF #008/208) to the time of baseline scan (CRF #160, screening CRF).

4.2.2. Medical History Variables

- Myocardial Infarction (MI) (yes, no). If yes, number of months from most recent MI to date of screening
- Stroke (yes, no). If yes, number of months from most recent stroke to date of screening

- Transient Ischemic Attack (TIA) (yes, no). If yes, number of months from most recent TIA to date of screening
- Evidence of Coronary Disease (CD) (yes, no). At least one of the following: unstable angina, stable angina, CABG surgery, Coronary PTCA/Atherectomy/PCI
- Deep Vein Thrombosis (DVT) (yes, no). If yes, number of months from most recent episode to date of screening
- Pulmonary Embolism (PE) (yes, no). If yes, number of months from most recent episode to date of screening
- Severe Peripheral Vascular Disease (yes, no)
- Disseminated Intravascular Coagulation (yes, no)
- Atrial Fibrillation (AF) (yes, no)
- Congestive Heart Failure (CHF) (yes, no). If yes, number of months from most recent hospitalization for CHF to date of screening
- Hypertension (yes, no)
- Hyperlipidemia (yes, no)
- Diabetes (yes, no)
- Renal Dysfunction (yes, no)
- Cancer (yes, no). If yes, primary site
- Chronic Anemia (yes, no)
- Bleeding (other than the current bleeding) (yes, no). If yes, number of months since most recent bleeding.
    - Upper gastrointestinal (yes, no)
    - Lower gastrointestinal (yes, no)
    - Urinary tract (yes, no)
    - Intracranial (yes, no)
    - Other (yes, no)
- GI Angiodysplasia (yes, no)
- Peptic Ulcer (yes, no)
- Diverticulitis (yes, no)
- Inflammatory Bowel Disease (yes, no)
- Helicobacter Pylori (yes, no)
- History of Tobacco Use (yes, no)

- Current Tobacco User (yes, no).

4.2.3. Details of Initial Hospitalization

- Time From Hospitalization to First Dose of andexanet (hours)
- Location of patient at time of enrollment (i.e., Emergency Department, Intensive Care Unit, Inpatient Ward, Stroke Unit, Other).

4.2.4. Vital and Hemodynamic Compromise Signs at 3 hours and at 15 Minutes Before Bolus

- Systolic Blood Pressure (mmHg); Diastolic Blood Pressure (mmHg), Pulse rate (bpm), Respiration rate (breath/min), Body temperature (degrees Celsius)
- Hemodynamic Compromise (yes, no), if yes report the following:
  - Poor Skin Perfusion (yes, no)
  - Mental Confusion (yes, no)
  - Hypotension (yes, no)
  - Low Urine Output (yes, no)
  - Dyspnea (yes, no)
  - Sweaty (yes, no)
  - Unconscious (yes, no)
  - Cold/clammy skin (yes, no)
  - Other (yes, no)

4.2.5. Factor Xa Inhibitor Treatment

- Factor Xa inhibitor: Rivaroxaban, Apixaban, Edoxaban, Enoxaparin, Unknown
- Total daily dose (mg)
- Estimated time from last dose to first dose of andexanet (hours)
- Indication for Factor Xa inhibitor (**see CRF 204, screening**)
  - Atrial Fibrillation (yes, no)
  - Venous Thromboembolism Prevention (yes, no)
  - Venous Thromboembolism Treatment (yes, no)
  - Acute Coronary Syndrome (yes, no)
  - Arterial Thromboembolism (yes, no). Note to programmers: Please note that arterial thromboembolism may have being reported as other.

- Other (yes, no)

- Duration of anticoagulation treatment prior to the screening assessment (days) (1 month = 30 days)

4.2.6. Medications within 7 Days Prior to Screening

Frequency distributions of the number of patients reporting medications by medication group and generic name (if applicable) within medication group will be presented for the following medication classes:

- Anti-platelet
- NSAIDs

4.2.7. Hematology within 3 hours and within 15 minutes of Bolus

- Hemoglobin (mmol/L)
- Hematocrit (%)
- Platelet count (10^9/L)

4.2.8. Coagulation and Biochemistry within 3 hours of Bolus

- INR
- Prothrombin time (sec)
- Fibrinogen (g/L)
- Potassium (mmol/L)
- Creatinine (mg/dL)
- Creatinine Clearance By Cockcroft-Gault (ml/min)
- ALT (U/L)
- AST (U/L)
- Total Bilirubin (µmol/L)
- Alkaline Phosphatase (U/L)
- Direct Bilirubin (µmol/L)

4.2.9. Pre-dose Treatment of Bleeding Episode

- Platelet Transfusion (yes, no). If yes, number of Units
- Coagulation Factor Transfusion (yes, no)
- Prothrombin complex concentrate (PCC) (yes, no)
- Hemostatic Treatments (yes, no)

- Packed Red Blood Cell Transfusion (yes, no)
- Use of Colloids and Crystalloids (yes, no)
- Other blood/coagulation-related Treatment (yes, no)

4.3. Primary Efficacy Endpoints

The two co-primary efficacy endpoints are the decrease in anti-fXa activity following andexanet treatment and the achievement of hemostatic efficacy. Anti-fXa activity will be evaluated at baseline, EOB, and at EOI, 4, 8, and 12 hours post-treatment. Anti-fXa activity will be expressed as ng/mL for apixaban, rivaroxaban, and edoxaban, and in IU/mL for enoxaparin.

The anti-fXa activity will be evaluated for the co-primary endpoint using percent change from baseline to on-treatment nadir.

The median percent change and 95% confidence intervals will be calculated separately for each FXA inhibitor.

The following variables will be calculated:

- On treatment Nadir: The on treatment nadir is the minimum value observed during treatment administration (i.e., minimum of EOB and EOI).
- Change from Baseline to On treatment Nadir: Change from baseline to On treatment Nadir is the reduction in anti-fXa activity from baseline to the minimum value during treatment administration (i.e., minimum value of EOB and EOI).
- Percent Change from Baseline to On treatment Nadir: The percent change from baseline to On treatment Nadir is the ratio between the Change from Baseline to On treatment Nadir, and the baseline, multiplied by 100.
- Percent Change from Baseline: The percent change from baseline is the ratio between the maximum change from baseline and the baseline, multiplied by 100.
- Percent Change from Baseline to EOI: The percent change from baseline to the EOI is the ratio between the Change from baseline to the EOI and the baseline, multiplied by 100.
- 12 hour Nadir: The 12 hour nadir is the minimum value observed post start of treatment evaluations (i.e., EOB to 12 hours post start of andexanet treatment).
- Area Under the Curve (AUC) for anti-fXa activity at each time point up to the 4 hours post end of infusion. The AUC will be calculated using trapezoid rule as follows:
    - Trapezoidal area calculation = ½ * (PCAFXa(x2) + PCAFXa(x1)) * (Time(x2) - Time(x1)), where PCAFXa = Anti-fXa; X1 is first or earlier time point and X2 is second time point.

Hemostatic efficacy will be determined by the blinded EAC as excellent, good, poor/none, not evaluable due to administrative reasons, or not evaluable due to clinical issue based as described

in the study protocol and Endpoint Adjudication Charter. Hemostatic efficacy will be presented as follows:

- Excellent
- Good
- Poor/None
- Not Evaluable

Effective hemostasis will be further defined as:

- 0 = patients with hemostatic efficacy rated by the EAC as poor/none
- 1 = patients with hemostatic efficacy rated by the EAC as excellent or good.
- 2 = Not evaluable due to non-administrative reason
- 3 = Not evaluable due to administrative reason.

4.4. Secondary Efficacy Endpoint

The secondary objective is to assess the relationship between anti-fXa activity and hemostatic efficacy. The anti-fXa activity will be evaluated as nadir (on treatment nadir), 12 hours nadir, absolute change from baseline, percent change from baseline, and the AUC for the anti-fXa activity as described above for the primary endpoint.

Hemostatic efficacy will be based on the outcome of adjudication as described above for the primary endpoint.

4.5. Other Efficacy Endpoints

4.5.1. Free Fraction of the FXa Inhibitor

The free fraction plasma concentration (ng/mL; also called the unbound plasma fraction) of apixaban, rivaroxaban, and edoxaban will be evaluated at Baseline (prior to andexanet treatment), and at EOB, EOI, 4, 8, and 12 hours after the EOI. In addition, % Protein Binding and Total Plasma Concentration (ng/mL) will be determined.

Change and percent change from baseline in free fraction of the inhibitor to the minimum value during andexanet treatment administration (i.e., minimum value between (EOB and EOI), and to each time point will be calculated. Values reported as <0.03125 will be replaced with 0.03125.

4.5.2. Tissue factor pathway inhibitor (TFPI)

TFPI parameters were collected, starting with Protocol Amendment 4 at baseline, EOI, 4, 8, 12, 24, 48, and 72 hours, and 7 days post andexanet treatment. TFPI Activity, Free TFPI antigen, and Total TFPI antigen will be determined.

Values < 0.2 will be replaced with ½ of LLOQ (i.e., 0.1). TFPI parameters will also be summarized as part of the safety analysis.

4.5.3. Thrombin Generation

Thrombin generation plasma samples were taken at Baseline, 8, 12, with additional samples (EOB, EOI, 4, 18, 24, 72 hours post infusion, and Day 30) collected starting with Protocol Amendment 4. Thrombin generation will be performed at a Central Laboratory. Five parameters related to thrombin generation are measured: Endogenous Thrombin Potential (ETP), peak height, time to peak height, lag time, and velocity index. Also, non-tissue factor ETP, lag time, peak height, time to peak height, and velocity index will be evaluated. Endogenous Thrombin Potential (ETP).

Endogenous Thrombin Potential (ETP) and non-tissue factor ETP are prospectively identified as the primary measure for thrombin generation.

Change and percent change from baseline for Endogenous Thrombin Potential to peak concentration and for non-tissue factor ETP will be calculated, and change from baseline for each time point will be calculated. Peak is the largest value between end of andexanet bolus and ending of infusion for each subject. For values identified by the lab as "BMC" will be replaced with zeros. Values identified as "AMC" will be replaced with blank (i.e., missing).

4.5.4. Antithrombin III (ATIII)

ATIII was collected starting Protocol Amendment 4 at baseline, EOI, 4, 8, 12, 24, 48, and 72 hours, and 7 days post andexanet treatment.

4.5.5. Anti-factor IIa Levels

Anti-factor IIa levels (pre- and post-administration of andexanet will only be collected for patients treated with enoxaparin. Values reported as < 0.04 will be replaced with 0.02.

4.5.6. Glasgow Coma Score (GCS)

The GCS will be evaluated only for ICH patients. Ideally the initial assessment would be made in the pre-morbid state, which is not possible within the context of this study. Therefore, the assessment will be performed at baseline, at 1 hour, 12 post the end of andexanet infusion, and at Day 30 follow-up. Each patient will be rated for all three domains (i.e., Eye Opening, Verbal Response, and Best Motor Response) in a scale of 1 to 6 as described below:

Score	Criterion
Eye Opening	
4	Open before stimulus
3	After spoken or shouted request
2	After fingertip stimulus
1	No opening at any time, no interfering factor
NT	Closed by local factor
Verbal Response	
5	Correctly gives name, place, and date
4	Not orientated but communication coherently
3	Intelligible single words
2	Only moans/groans
1	No audible response, nom interfering factor
NT	Factor interfering with communication
Best Motor Response	
6	Obey 2-part request
5	Brings hand above clavicle to stimulus on head/neck
4	Bends arm at elbow rapidly but features not predominantly abnormal
3	Bends arm at elbow, features clearly predominantly abnormal
2	Extends arm at elbow
1	No movement in arms/legs, no interfering factor
NT	Paralyzed or other limiting factor

NT = Not testable

The individual scores from each item are summed in order to calculate a patient's total GCS score. The maximum possible score is 15, with the minimum score being of 3.

Note to programmer, because the "NT" can be analyzed in multiple ways, individual scores for eye opening, verbal and motor response should be presented.

4.5.7. Modified Rankin Score (mRS)

The mRS will be evaluated only for ICH patients. Ideally the initial assessment would be made in the pre-morbid state, which is not possible within the context of this study. Therefore, the assessment will be performed at baseline, at 1 hour, 12 post the end of andexanet infusion and at Day 30 follow-up. The scale runs from 0 to 6, running from perfect health without symptoms (0) to death (6).

- 0 - No symptoms at all.
- 1 - No significant disability. Able to carry out all usual duties and activities, despite some symptoms.

- 2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
- 3 - Moderate disability. Requiring some help, but able to walk without assistance.
- 4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- 5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
- 6 - Dead.

mRS will be further defined at each time point as follows:

- 1 = for patients with of zero to 2, inclusive, and
- 0 = for patients with score greater than 2.

4.5.8. National Institutes of Health Stroke Scale (NIHSS)

The NIHSS will be evaluated only for ICH patients. Assessment will be performed at baseline, at 1 hour, 12 post the end of andexanet infusion and at Day 30 follow-up. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The overall severity of stroke can be interpreted as follows:

NIHS Score	Stroke Severity
0	No stroke symptoms
1-4	Minor stroke
5-15	Moderate stroke
16-20	Moderate to severe stroke
21-42	Severe stroke

The individual scores from each item are summed in order to calculate a patient's total NIHSS. The maximum possible score is 42, with the minimum score being of 0. For handling of missing values, refer to Section 5.5.3 of this document.

4.5.9. ICH Score

The ICH Score is a clinical grading scale designed for risk stratification of patients after acute non traumatic intracerebral hemorrhage (ICH) [2]. The total ICH Score (is the sum of the points of the various characteristics as indicated below.

Component	Levels	ICH Score Points
GCS	3 -4	2
	5 - 12	1
	13 - 15	0
ICH Volume	≥ 30 cm^3	1
	< 30 cm^3	0
Intraventricular Hemorrhage (CRF#160)	Yes	1
	No	0
Infratentorial origin of ICH (CRF#160)	Yes	1
	No	0
Age	≥ 80 years	1
	< 80 years	0

ICH Volume is calculated using the formula ABC/2, where A is the greatest diameter of the hematoma on the slice with the largest diameter, B is the diameter of the hematoma in the axis perpendicular to A, and C is the number of axial slices in which the hematoma is visible, multiplied by the slice thickness. See CRF #160 for 'Intra-ventricular hemorrhage' 'Intracerebral hemorrhage' 'Intracranial hemorrhage' for hematoma volume.

For Infratentorial origin of ICH reply yes, if faobj='Infratentorial bleed' and FAORRES='Yes'.

4.6. Safety Endpoints

4.6.1. Exposure

- Planned Andexanet Dose
- Andexanet Dose Received
- Was the Treatment Modified (yes, no)
- Reason for Treatment Modification:
  - Treatment was not Modified
  - Withdrawal of Consent
  - Intolerable AE/SAE that cannot be ameliorated by appropriate medical intervention
  - AE/SAE that in the Investigator's opinion would lead to undue risk
  - Infusion Reaction
  - Other
- Treatment Modification
  - Treatment was not Modification

- Rate Increased
- Rate Decreased
- Discontinued
- Interrupted

4.6.2. Infusion Reaction (CR # 054)

- Patient had an Infusion Reaction (yes, no)
- Duration of the Infusion Reaction (minutes)
- Time from Start of Andexanet Administration to the Reaction (minutes)
- Infusion Reaction Symptom
- Was the Treatment Modified (yes, no)
- Treatment Received for Infusion Reaction

4.6.3. Use of Red Blood Cell Transfusions

- Were Blood Products and Hemostatic Agents used Post Treatment (yes, no)

4.6.4. Re-bleeding

Re-bleeding is defined as bleeding from the same or another anatomical site in the patient within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. Re-bleeding will be adjudicated by the EAC. The following variables will be analyzed:

- Did Re-bleeding Occur (yes, no)
- Site of Re-bleeding
- Start Date/Time of Re-bleeding
- Stop Date/Time of Re-bleeding
- Time to Re-bleeding: Numbers of days/hours from date time of first dose of andexanet treatment to the time of Re-bleeding.
- Treatment Received for Re-Bleeding
- Coagulation Factor Transfusion (yes, no)
- Hemostatic Treatments (yes, no)
- Packed Red Blood Cell Transfusion (yes, no)
- Use of Colloids and Crystalloids (yes, no)
- Other blood/coagulation Related Treatment (yes, no)

4.6.5. Death

- Did the Patient Die (yes, no)
- Date/time of Death
- Time to Death: Number of days/hours from inform consent to death.
- Cause of Death; Adjudicated cause of death will be first grouped as cardiovascular or Non-cardiovascular as adjudicated by the EAC. In addition, the sub-category as presented in CR#099 for Cardiovascular or non-cardiovascular reason need to be specified.
- Death Preceded by Myocardial Infarction, Ischemic Stroke (note to programmer: ischemic stroke sometimes was reported as Embolic Stoke), Deep Vein Thrombosis, Pulmonary Embolism, and/or Arterial Systemic Embolism.

4.6.6. Hospitalization

Hospital Length of Stay (LOS): Duration of the index hospitalization. The following steps will be followed to calculate the LOS:

- The LOS will be calculated as the discharge date/time minus the admission date/time plus 1.
- If patient admission time and the discharge time is missing and the dates are the same, the LOS will assumed to be 1 day.
- If patient admission time and the discharge time is missing and the dates are not the same, the LOS will calculated using the date portion of the dates plus 1.
- If the discharge date is missing, and no new admission date, the date of the 30-day visit, the date of death, or 37 days after enrollment (whichever is earliest) will be imputed as the discharge date and calculate the LOS for the given stay.
- If a patient has withdrawn consent, exclude the patient from analysis of hospital LOS.

4.6.7. Anticoagulation Treatment

Anticoagulation treatment is reported as part of the concomitant medication and occur prior to treatment, and at any time post treatment. The determination of whether a patient has resumed anticoagulant treatment after andexanet administration will be characterized with two complementary methods as follows:

- Patients receiving any anticoagulant therapy given after andexanet treatment, either parenterally (e.g., enoxaparin, dalteparin, heparin, certoparin, nadroparin, fondaparinux) or orally (e.g., warfarin, rivaroxaban, apixaban, edoxaban, dabigatran, phenprocoumon, phenindione) for any duration at any dose up to the 30-day follow visit.
- Patients receiving any oral anticoagulant starting after the initiation of the andexanet bolus, and continuing for the duration of the follow-up period through either the Day 30

visit or death. Note – for patients enrolled prior to the implementation of Protocol Amendment 4 (for whom date of discontinuation was not indicated in the database), derivation rules will be specified.

In addition to the above, the following variables will be analyzed:

- Indication for Anticoagulation: Patients may receive anticoagulation for multiple reasons. Indication will be defined as follows:
  - Arterial Thromboembolism: Any concomitant medication with indication term that contains "Arterial Thromboembolism, CVA, Secondary Stroke, Cerebrovascular Accident, PAD, Clot Related to Transplant Kidney/Pancreas."
  - Atrial Fibrillation
  - VTE: Any concomitant medication with indication term that contains "Venous Thromboembolism Prevention, Venous Thromboembolism Treatment, Pulmonary Embolism."
  - Other: Any concomitant medication with indication term that contains "ARTIFICIAL HEART VALVE, PORTAL VENOURS THROMBOSIS, S/P CABG WITH MAZE PROCEDURE FOR A-FIB, STROKE, PACEMAKER, ATRIAL FLUTTER, THROMBOPHLEBITIS, GUILLAIN-BARRE SYMDROME, THROMBOCYTHEMIA, THROMBOPHILIA, ARRHYTHMIA, ATRIAL FLUTTER, BRIDGING OF COUMADIN FOR MVR-S/P LAMINECTOMY, MECHANICAL MITRAL AND AORTIC VALVE, TRANSTHYRETIN AMYLOIDOSIS, PERIPHER VASCULAR DISEASE + STENT."
- Start Date and Time for Anticoagulation: Date and Time of first anticoagulation prior to andexanet treatment
- Number of Hours from Anticoagulation: Numbers of hours from last dose of anticoagulation to start of andexanet dose
- Start Date and Time for Re-anticoagulation: Date and Time of first anticoagulation post start of andexanet treatment. If time is missing, report only the date.
- Number of Days to Re-Anticoagulation: Numbers of days from first dose of andexanet to re-start of anticoagulation treatment (no days = intck('day', date of first andexanet dose, date re-start anticoagulation).
- Was the Re-anticoagulation Dose Therapeutic (yes, no)
- Reason for Re-anticoagulation (see reason on CR#230, include therapeutic and non-therapeutic reasons. For other, use other non-therapeutic or other therapeutic)

4.6.8. Thrombotic Events

Thrombotic events (TE) will be adjudicated by the EAC (see CRF#122). A patient may have multiple Thrombotic events.

- Adjudicated Thrombotic events will be rated as follows:
  - 0 = If the event type is adjudicated as Death or Other AE. These events are not considered to be TEs.
  - 1 = If the event type is adjudicated as Myocardial Infarction; Ischemic Stroke (Stroke with adjudicated code of 021 for Ischemic), Transient Ischemic Attack, Deep Vein Thrombosis, Pulmonary Embolism or Arterial Systemic Embolism) and the adjudication decision is "Agree". These events are considered to be TEs.
- Thrombotic Event Type: Defined based on CRF#122 and coded as follows:
  - CVA = Ischemic Stroke
  - MI = Myocardial Infarction
  - DVT = Deep Vein Thrombosis
  - PE = Pulmonary Embolism
  - ASE = Arterial Systemic Embolism
  - TIA= Transient Ischemic Attack.
- Date and Time of Thrombotic Event
- Time to Thrombotic Event: Time elapsed from first dose of andexanet treatment to the Date time of TE. Time to thrombotic events will be calculated in hours and days. Time to Thrombotic Event will also be presented as categorical variable. The following categories will be used: 0-12 hours; >12 hours and < 4 days; 4 to 30 days.

Per correspondence with FDA during label negotiations prior to FDA approval of the label supplement on 06 March 2020, an additional definition of Thrombotic Events includes the following list of adverse event terms:

- "Acute myocardial infarction"
- "Myocardial infarction"
- "Myocardial ischaemia"
- "Troponin increased"
- "Troponin T increased"
- "Cardiac arrest"
- "Cardio-respiratory arrest"
- "Cardiac failure"
- "Cardiac failure congestive"
- "Right ventricular failure"
- "Cardiac ventricular thrombosis"
- "Cerebrovascular accident"
- "Death"
- "Deep vein thrombosis"
- "Embolism venous"
- "Venous thrombosis limb"
- "Intracranial venous sinus thrombosis"
- "Ischaemic hepatitis"
- "Pulmonary embolism"
- "Acute respiratory failure"
- "Respiratory failure"
- "Embolic stroke"
- "Ischaemic stroke"
- "Sudden death"

- "Cardiogenic shock"
- "Cerebellar infarction"
- "Cerebellar ischaemia"
- "Cerebral infarction"
- "Transient ischaemic attack"
- "Ventricular tachycardia" "Iliac artery occlusion" "Heparin-induced thrombocytopenia"

5.0 STATISTICAL METHODS

5.1. General Considerations

All hypothesis tests will be 2-sided and reported at the 0.05 significance level. All CIs will be 2-sided and reported at the 95% confidence level unless stated otherwise. P-values will be rounded to 3 decimal places. P-values less than 0.001 will be presented at $p < 0.001$.

For continuous variables, the number of non-missing observations, mean, median, quartiles, standard deviation, minimum, maximum, and 95% confidence interval (CI) will be presented unless stated otherwise. Means, medians, quartiles, and 95% CI will be displayed to 1 more decimal place than the raw data and the standard deviation will be displayed to 2 more decimal places. The minimum and maximum will be displayed to the same number of decimal places as reported in the raw data. For categorical variables, the number of observations, the number of events, and percentages of events with the 95% CI will be reported. Descriptive summaries will be presented for the efficacy population as well as for the individual subgroup analyses.

It is anticipated that all statistical analyses will be performed using SAS Version 9.4 (SAS Institute, Inc., Cary NC) or higher. Additional software may be used for the production of graphics and for statistical methodology not provided by SAS. All summaries and analyses documented in this Statistical Analysis Plan (SAP) will be presented in the final integrated CSR. The CSR may also contain additional tables or statistical tests as warranted by the data obtained. The justification for any such additional analyses will be fully documented in the CSR.

5.2. Analysis Populations

5.2.1. Safety Population

The Safety Population will consist of all patients treated with any amount of andexanet.

5.2.2. Efficacy Population

The Efficacy Population will include all patients in the Safety Population who meet all of the following criteria:

- Are determined by the EAC to meet the clinical bleeding inclusion criteria.
- Have a baseline anti-fXa level
- Baseline anti-fXa level of at least 75 ng/mL for apixaban and rivaroxaban, 40 ng/mL for edoxaban, and 0.25 IU/mL for patients receiving enoxaparin.

5.2.3. High Risk ICH Population

The High Risk ICH analysis population will include all ICH patients in the efficacy Population with any of the following:

- For intracerebral/intraparenchymal bleeding, volume of hematoma > 3 cc.

- For subdural bleeding, thickness of hematoma > 10 mm or midline shift > 5 mm.
- For subarachnoid bleeding, thickness of hematoma > 10 mm.

5.3. Appropriateness of Primary Efficacy Endpoints

Anti-fXa activity is considered a biomarker reasonably likely to predict clinical benefit based on the following data:

- The direct FXa inhibitors have similar structural, stoichiometric, pharmacokinetic (PK), and functional properties.
- Anti-fXa activity is a direct measure of the inhibition of the enzymatic activity of FXa by anticoagulants in the FXa class and correlates with the plasma concentrations of rivaroxaban, apixaban, and edoxaban (e.g., 100 ng/mL of plasma apixaban = 100 ng/mL anti-fXa activity of apixaban).
- Data from the clinical studies of currently approved direct FXa inhibitors (apixaban, rivaroxaban, edoxaban) clearly demonstrate a correlation between plasma concentrations of the FXa inhibitor and increased bleeding.
- Data from both the FXa inhibitor clinical studies and the andexanet clinical program demonstrate a 1:1 correlation between FXa inhibitor concentrations and anti-fXa activity.
- In both nonclinical and clinical studies, increases in anti-fXa activity correlate with decreases in thrombin generation.
- There is consistency across all three direct FXa inhibitors regarding the correlations between anti-fXa activity levels and free-fraction of the inhibitors, thrombin generation, and the Activated Clotting Time (ACT) in the andexanet clinical studies.
- In animal models of anticoagulant-exacerbated bleeding, reduction in anti-fXa activity correlates with reduction in blood loss.

For Hemostatic efficacy assessment, because of the heterogeneity of bleeding (e.g., different anatomic locations, different mechanism and severity of injury), it was not possible to use a single type of measurement to evaluate all bleeding types. The efficacy variable of "effective hemostasis" (Protocol Amendment 4 Appendix B) chosen for this study was an endpoint developed in collaboration with the FDA and agreed to by the Committee for Medicinal Products for Human Use (CHMP) during scientific advice received in 2014. The criteria for this endpoint were based on those used in the study by Sarode, et al (2013) [1], which was a registration trial for a reversal agent for warfarin-induced bleeding. The scoring system for effective hemostasis allows for different types of assessments for different bleeding types (e.g., head CT or MRI for ICH, corrected Hb and hematocrit for non-visible bleeding, and clinical assessments for visible, muscular, and skeletal bleeding). Because the criteria for determination of hemostatic efficacy are largely based on objective measures (CT/MRI measurements, Hb corrected for transfusion), the potential for bias is reduced (to further reduce the potential for bias, bleeds that were more

dependent on subjective assessments of clinical hemostasis [i.e., musculoskeletal bleeds, intra-articular bleeds, visible bleeds] were excluded with the implementation of Protocol Amendment 4). In addition, an independent EAC adjudicated all endpoints blinded to the results of the anti-fXa evaluation.

5.4. Adjustment for Covariates

No adjustment for covariates will be performed.

5.5. Handling of Dropouts and Missing Values

5.5.1. Anti-fXa Activity

For patients treated with apixaban, rivaroxaban, and edoxaban, anti-fXa values greater than 950 ng/mL the anti-fXa value will be replaced with 950. If the anti-fXa value is < 4.0 ng/mL then the value will be replaced with 4.0. For enoxaparin treated patients, anti-fXa values identified as < 0.10 IU/mL will be replaced with 0.10.

If the baseline anti-fXa activity is missing, the patient will be excluded from the efficacy analysis population. For post baseline assessments, if both the EOB and EOI assessments are missing, the maximum change will be replaced with zero (i.e., no change from baseline) and the Nadir will be replaced with the baseline value using the Baseline Observation Carried Forward principle (BOCF principle). If only one post-baseline sample is missing, the available sample (either EOB or EOI) will be used for the imputation (Last Observation Carried Forward [LOCF]).

5.5.2. Hemostatic Efficacy

For primary efficacy analysis, missing values (i.e., rated as Non-Evaluable due to administrative reasons) will be excluded from analysis. On the other hand, missing values due to non-administrative reason will be considered as treatment failure.

Non-evaluable for administrative reason is defined in the EAC Charter. The final decision regarding whether a patient is non-evaluable due to administrative or non-administrative reasons will be made by the EAC.

A sensitivity analysis will be performed with all patients rated as Non Evaluable classified as not reaching hemostatic efficacy.

5.5.3. NIHSS

Analysis will be performed only for the baseline and 12 hours post treatment. If the baseline or the 12-hour post-treatment NIHSS score is missing, the patient will be excluded from analysis.

5.5.4. Ambiguous Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range

will be taken. In the case where a patient records more than one score for any particular measure, the worst of the recorded scores will be taken for analysis purposes. In all cases, sites will be queried first to determine whether a more precise value is available.

5.6. Multiple Investigator Sites

Sites will be grouped according to the Region as North America and Europe.

5.7. Multiple Comparisons/Multiplicity

No adjustment is planned for multiple secondary endpoints. Secondary analyses and secondary outcomes will be treated as 'exploratory' analyses to assess the consistency of the primary efficacy analysis.

5.8. Use of Efficacy Subset

As defined in the previous section, primary analyses will be performed using the efficacy analysis population. In addition, primary efficacy analysis will be performed by sex, age category, country, bleeding type, FXa Inhibitor, andexanet manufacturing process, and andexanet dose.

5.9. Data Derivation

- The following derivation rules will apply: unless missing data is imputed using the imputation methods described above, all tabulations involving change from baseline data will only include subjects with cohort data i.e. with data at baseline and at follow-up. Change from baseline will be calculated as follow-up values minus baseline value. Percentage changes from baseline will be rounded to 1 decimal place.
- For analysis purposes, 1 month = 30 days and duration in months will be rounded to 1 decimal place.
- Any derived data recorded in hours will be rounded to 1 decimal place.
- All calculation of length of time, including age, should be performed using SAS function to account for leap year.
- Height in inches will be converted to centimeters by multiplying by 2.54 and rounding to the nearest integer.
- Weight in lbs will be converted to kg by dividing by 2.2046 and rounding to 1 decimal place.
- Body mass index (BMI) will be calculated as weight (kg) / (height (cm)/100)^2 rounded to 1 decimal place.
- Temperature in Fahrenheit will be converted to Celsius by subtracting 32 and dividing by 1.8.

- Hemoglobin in g/L will be converted to mmol/L by multiplying by 0.06206 and rounding to 2 decimal places.
- To convert from g/dL to g/L multiply by 10.
- To convert from mg/dL to g/L multiply by 0.01 and round to 2 decimal places.
- To convert from mEq/L to mmol/L multiply by 1.
- To convert from µkat/L to U/L multiply by 1.
- For white blood cell and platelet count then $10^9/L = 10^3/mm^3$.
- For each white blood cell differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) to convert from % to $10^9/L$ by multiplying the value by the WBC ($10^9/L$) and dividing by 100 and rounding to 1 decimal place.
- For creatinine to convert from µmol/L to mg/dL divide by 88.4173 and round to 1 decimal place.
- For serum glucose to convert from mmol/L to mg/dL divide by 0.0555 and round to 1 decimal place.
- For blood urea nitrogen to convert from mmol/L to mg/dL divide by 0.3651 and round to 1 decimal place.
- For total and direct bilirubin to convert from µmol/L to mg/dL to µmol/L divide by 17.0999 and round to 1 decimal place.
- For calcium to convert from mmol/L to mg/dL divide by 0.2495 and round to 2 decimal places.
- For phosphorous to convert from mmol/L to mg/dL divide by 0.3229 and round to 2 decimal places.
- For plasma concentrations that are lower than lower level of quantification (LLOQ) then the value will be taken as LLOQ threshold value.
- For plasma concentrations that are higher than the upper level of quantification (ULOQ) then the value will be taken as ULOQ threshold value.

5.10. Statistical Analysis

5.10.1. Subject Disposition

The number of patients included in the safety and efficacy populations will be tabulated. In addition, the disposition of patients who completed the study and who discontinued from the study will be presented. The reason for discontinuation from the study will be presented in a listing in Section 4.1.1.

5.10.2. Inclusion Criteria

A list of andexanet-treated patients not meeting one or more inclusion criteria will be presented.

5.10.3. Exclusion Criteria

A list of andexanet-treated patients meeting one or more exclusion criteria will be presented.

5.10.4. Protocol Deviations

Protocol deviations will be listed. Specific protocol deviations include the following:

- Those who entered the study even though they did not satisfy the entry criteria.
- Those who developed withdrawal criteria during the study but were not withdrawn.
- Those who received the wrong treatment or incorrect dose.
- Those who received an excluded concomitant treatment.

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

Per the protocol, the percent change from baseline in anti-FXa activity to the nadir will be defined by a specific evaluation period as the period starting 3 minutes after the start of the andexanet bolus and ending 5 minutes after the end of the andexanet infusion. Acceptable windows around these times are defined in the Protocol (Appendix A, Schedule of Activities).

Samples drawn outside these windows may be considered significant protocol deviations, especially if they impact the integrity of the data. The protocol deviations may also be presented in a listing.

5.11. Treatment Compliance

Patient compliance with the andexanet treatment will not be evaluated as the treatment is performed in the hospital by a trained professional. The total dose of andexanet administered to each subject and the time from last dose of FXa Inhibitor to the start of andexanet for bolus will be summarized. In addition, any treatment modification and the reason for modification will be tabulated.

5.11.1. Demographic and Baseline Characteristics

Baseline and demographic characteristics such as such as age (years), weight (kg), height (cm), body mass index (BMI in kg/m^2), ethnicity, race, sex, GCS, mRS, NIHSS, ICH score, Factor Xa Inhibitor, baseline hematology, chemistry, vital signs, medical history, mechanism of injury (spontaneous or traumatic), and ICH imaging characteristics (e.g., volume, thickness, midline shift, intraventricular involvement, supratentorial vs. infratentorial location) will be summarized

for both the safety and efficacy populations. Description of variable to be summarized are presented in Section 4.2.

For continuous variables, number of observations, mean, median, standard deviation, and minimum and maximum values will be presented. For categorical variables, counts, percentages will be tabulated for each category.

All available data will be included in the analysis. Missing values will not be imputed.

5.12. Concomitant Therapy

All medication used following informed consent through End of Study (Day 30) will be documented. Prior medications that are ongoing at the time of study enrollment are also recorded. All concomitant medications will be listed.

5.13. Efficacy Analysis

All efficacy analyses will be performed separately for each FXa inhibitor (i.e., apixaban, rivaroxaban, edoxaban and enoxaparin). In certain cases, a pooled analysis will be provided as well, and is indicated below where appropriate.

5.13.1. Primary Efficacy Analysis

Two primary endpoints will be evaluated:

- The percent change from baseline in anti-fXa activity to the on treatment nadir (i.e., minimum value between EOB and EOI).
- The achievement of hemostatic efficacy of stopping an ongoing major bleed at 12 hours from the end of the andexanet infusion, rated by the independent EAC as excellent or good.

The first objective is to demonstrate the decrease in anti-fXa activity following andexanet treatment. Analysis will include all patients in the efficacy population. The following hypothesis will be evaluated:

H_0: $\mu = 0$

H_1: $\mu \neq 0$

The percent change in anti-fXa activity from baseline (last measurement before administration of andexanet) to post administration (the lowest level measured between the start of andexanet administration and 10 minutes after the end of the andexanet administration) will be calculated for each patient as %change = 100 × (post – baseline) / baseline rounded to 1 decimal place. Percent change from baseline in anti-fXa activity will be evaluated using a distribution free two-

sided 95% CIs for the median. Because the data are expected to be non-normal, the distribution free confidence interval will be the primary for decision making. If the CI for the median excludes 0, the first primary objective will be considered to have been met. The CI will be calculated using distribution free methods using PROC UNIVARIATE in SAS as shown below.

```
proc univariate ciquantdf (alpha=.05);

  var val;

  ods output Quantiles=results;

run;
```

The second primary objective is to evaluate the hemostatic efficacy following andexanet treatment. Analysis will be performed including all patients in the efficacy population with valid EAC hemostatic efficacy adjudication (excluding events adjudicated as non-evaluable due to administrative reason). In addition, a sensitivity analysis will be conducted with the patients adjudicated as non-evaluable due to administrative reason rated as poor hemostatic efficacy.

The following hypothesis will be evaluated:

H_0: $\pi = 0.50$

H_1: $\pi \neq 0.50$

The proportion of patients in the Efficacy Analysis Population who are adjudicated to have effective hemostasis (excellent or good) by the independent EAC will be summarized. An exact 95% CI will be reported. The study will be considered to have met its second primary efficacy objective if the proportion of patients with excellent or good hemostasis (as adjudicated by the independent Endpoint Adjudication Committee [EAC]) is statistically significantly higher than 50% ($p < 0.05$). This test will be performed by calculating the exact binomial confidence interval and checking that it only contains points above 0.5. In addition to the confidence interval the one sided (right) p-value from the exact binomial test that the lower bound of the confidence interval will be higher than 50% will be presented. In SAS this will use the exact binomial option in PROC FREQ as shown below.

```
proc freq;

tables val binomial (p=.50) noprint;

exact binomial;

output out=results binomial exact;

run;
```

To maintain the type I error rate, the decision on the second primary objective will only be made if the first primary objective is met. This results in a fixed sequence multiple comparisons procedure.

5.13.1.1. Sensitivity Analysis

Sensitivity analyses will be performed for two primary efficacy endpoints for patients who are otherwise efficacy evaluable but have baseline anti-fXa level of less than 75 ng/mL for apixaban and rivaroxaban, less than 40 ng/mL for edoxaban, and less than 0.25 IU/mL for patients receiving enoxaparin.

In addition, the primary efficacy analysis will be performed including all patients in the safety population with anti-fXa level at baseline.

5.13.1.2. Exploratory Analysis

Consistency of efficacy across important subgroups will be investigated. Analysis will be performed for the efficacy population. The two primary endpoints will be summarized for the following subgroups:

- Sex (Male, Female)
- Race (any race with at least 5 members, all other races combined)
- Age (< 65 years, 65–75 years, >75 years)
- FXa inhibitor (apixaban, rivaroxaban, edoxaban, enoxaparin)
- Bleed type (GI, ICH, Other)
- Dose of andexanet (low dose [400 mg bolus + 480 mg infusion], high dose [800 mg bolus plus 960 mg infusion])
- Region (North America, Europe, and Japan)
- Renal function (eGFR < 50 mL/min, eGFR ≥ 50 mL/min)

5.14. Secondary Efficacy Analysis

The secondary objective of the study is to assess the relationship between the change from baseline in anti-fXa activity and achievement of hemostatic efficacy in patients receiving an FXa inhibitor who have acute major bleeding and reduced FXa activity.

Analysis

A logistic regression model predicting the log-odds ratio of success of hemostatic efficacy (rated as "Excellent" or "Good"), with the anti-fXa level activity as a covariate will be used to determine the relationship between anti-fXa level and the clinical outcome.

A subset analysis on the Intracranial patients will be performed using a logistic regression with 2 additional covariates: the log of (the baseline ICH volume + 1), and an indicator variable for baseline Infratentorial involvement.

Anti-fXa Level Measurement

Hemostatic efficacy is achieved when the body has time to produce thrombin and a subsequent clot, thus the anti-fXa level during the first few hours after administration is more important than the decrease in anti-fXa level to predict the log-odds of success of hemostatic efficacy. Therefore, the on-treatment nadir value will be used in the analysis.

Standardization Across Inhibitors

The most power would be gained if it were possible to pool the data across all the anti-fXa inhibitors, however, anti-factor Xa activity levels cannot be combined in the same analysis due to the different bioavailability and pharmacokinetics of the individual FXa inhibitors, especially between the direct and indirect FXa inhibitors. An alternative way to use the activity level that would enable pooling the data is to convert the continuous measurements into a dichotomous variable indicating a level that has similar anticoagulant effects across the 4 different inhibitors.

For the DOACs, current guidelines by the subcommittee on control of anticoagulation of the International Society on Thrombosis and Hemostasis (ISTH) and the French Working group on perioperative hemostasis (GIHP) recommend using a value of 30 ng/mL to determine if antidote administration should be considered.[4, 5] Unfortunately there is no similar threshold for the indirect anticoagulants, therefore the threshold for the Enoxaparin patients in the analysis will be the lower limit of detection (0.10 IU/mL). Sensitivity analyses excluding patients taking Enoxaparin will be performed as well, with (1) the log of anti-fXa at on-treatment Nadir as a covariate, and (2) the dichotomous variable for anti-fXa less than the threshold as a covariate.

A summary of the planned analyses is below:

Model	Population	Reduced Model covariates	Full Model covariates
1	Efficacy, excluding patients with Non-Evaluable Hemostatic Efficacy due to Admin reason	None (intercept only model)	Indicator variable for on-treatment Nadir anti-fXa level < threshold*
2	Same as (1) except exclude Enoxaparin patients also	None (intercept only model)	Indicator variable for on-treatment Nadir anti-fXa level < threshold*
3	Same as (1) except exclude Enoxaparin patients also	None (intercept only model)	Log of on-treatment Nadir anti-fXa level

4	Same as (1) except exclude non-ICH patients also	Log of (baseline ICH volume +1), Indicator variable for Infratentorial involvement	Reduced Model covariates plus Indicator variable for on- treatment Nadir anti-fXa level < threshold*

*The threshold=30 ng/mL for Apixaban, Rivaroxaban and Edoxaban, and 0.10 IU/mL for Enoxaparin.

Descriptive statistics, odds ratios with the corresponding 95% confidence intervals, and p-values from the models will be presented. The Full Model will be compared to the Reduced Model with a Likelihood Ratio Test. The Reduced Model will be rejected in favor of the Full Model if the Likelihood Ratio Test p-value is <0.05.

The area under the receiver operating characteristic (AUC under ROC) with the 95% CI will be presented.

5.15. Additional Efficacy Analysis

The following additional efficacy endpoints will be evaluated:

5.15.1.1. Free Fraction of the FXa Inhibitor

The Free Fraction Plasma Concentration (ng/mL; also known as unbound plasma fraction) of apixaban, rivaroxaban, and edoxaban will be evaluated at Baseline (prior to andexanet treatment), and at EOB, EOI, 4, 8, and 12 hours after the end of andexanet infusion. In addition, % Protein Binding will be determined.

Change and percent change from baseline in Free Fraction of the inhibitor to the minimum value during andexanet treatment administration (i.e., minimum value between (EOB and EOI), and to each time point will be calculated. Mean, median, standard deviation, minimum, and maximum value, and 95% CI for the median will be presented. Confidence interval will be estimated using distribution free procedure as described above for primary efficacy analysis. In addition, the time course of unbound inhibitor concentrations following andexanet infusion will be presented. % Protein Binding will be presented as listings.

5.15.1.2. Thrombin Generation

Thrombin generation will be measured from plasma samples at Baseline, EOB, EOI, 4, 8, 12, 18, 24, 48, 72 hours post andexanet treatment, and Day 30. Five parameters related to thrombin generation will be measured: Endogenous Thrombin Potential (ETP), peak height, time to peak height, lag time, and velocity index.

ETP (nM*min) is prospectively identified as the primary measure for thrombin generation. The time course for ETP will be plotted for each FXa inhibitor. In addition, change and percent

change from baseline to peak ETP will be calculated, and change from baseline for each time point will be calculated. Peak is the largest value between end of andexanet bolus and ending of infusion for each subject. Mean, median, standard deviation, minimum, and maximum value, and 95% CI for the median will be presented. Confidence interval will be estimated using distribution free procedure as described above for primary efficacy analysis. Similar analysis will also be performed for Non-TF Endogenous Thrombin Potential.

The other Thrombin generation parameters (i.e., peak height, time to peak height, lag time, and velocity index, non TF ETP peak height, time to peak height, lag time, and velocity index) will be presented in a summary table for each time point and in a data listing by patient.

5.15.1.3. Tissue Factor Pathway Inhibitor (TFPI)

For patients enrolled under Amendment 4, TFPI will be collected at baseline (i.e., prior to andexanet treatment), EOI, 4, 8, 12, 24, 48, and 72 hours, and 7 days post andexanet treatment. TFPI Activity, Free TFPI antigen, and Total TFPI antigen will be determined.

Mean, median, standard deviation, minimum, and maximum value, and 95% CI for the median will be presented for each time. Confidence intervals will be estimated using a distribution free procedure as described above for the primary efficacy analysis.

5.15.1.4. Antithrombin III (ATIII)

For patients enrolled in Amendment 4, ATIII will be collected at baseline prior to andexanet treatment, EOI, 4, 8, 12, 24, 48, and 72 hours, and 7 days post andexanet treatment. Mean, median, standard deviation, minimum, and maximum value, and 95% CI for the median will be presented. Confidence intervals will be estimated using a distribution free procedure as described above for the primary efficacy analysis.

5.15.1.5. Anti-Factor IIa Activity

For enoxaparin patients, Anti-factor IIa levels (pre- and post-administration of andexanet will be collected. Outcome will be presented in a summary table for each time point and data listing by patient.

5.15.1.6. Hemostatic Efficacy in ICH Patients

Hemostatic efficacy following andexanet treatment will be analyzed including all patients in the efficacy population with ICH bleeding type with valid EAC hemostatic efficacy adjudication. The proportion of patients in the Analysis Population who are adjudicated to have effective hemostasis (excellent or good) by the independent EAC will be summarized. An exact 95% CI will be reported. Analysis will be performed for the overall ICH patient population and by age category, sex, region, FXa Inhibitor., and andexanet dose.

5.15.1.7. Use of Red Blood Cell Transfusions

The proportion of patients that received red blood cell transfusion after the start of andexanet treatment will be summarized for both the safety and efficacy populations. The proportion of patients that receive red blood cell transfusion and the Fisher exact 95% CI will be presented for the overall population, bleeding type, FXa inhibitor, andexanet manufacturing process and andexanet dose. In addition, the number of red blood cell units transfused per patient from the start of the andexanet bolus through 12 hours after the end of the andexanet infusion will be presented as data listing.

5.15.1.8. Use of other Blood Products and Hemostatic Agents

Use of blood product and hemostatic agents after the start of andexanet treatment will be provided as a data listing by patient.

5.15.1.9. Re-Bleeding

Re-bleeding data will be listed with FXa inhibitor, initial bleeding type, and andexanet dose.

5.15.1.10. Change in Clinical Neurologic Status for ICH Patient Population

Clinical neurologic status evaluation will be based on mRS, GCS, and the NIHSS scores. The primary goal of these scale analyses is to detect any clinical worsening in ICH patients. For the mRS, the number of patients with score of zero to 2, inclusive (i.e., qualified as success) and of patients with score greater than 2 as failure. The proportion of events and the 95% Fisher exact confidence interval will be presented for baseline, 1 hour after the end of the andexanet infusion, 12 hours after the end of the andexanet infusion, and at Day 30 follow-up. Exact 95% CI will be presented.

The GCS will be evaluated at baseline, at 1 hour after the end of the andexanet infusion, 12 hours after the end of the andexanet infusion, and at Day 30 follow-up. Each patient will be rated for all three domains (i.e., Eye Opening, Verbal Response, and Best Motor Response). The sum of the three domains score will be summarized as the raw value and change from baseline. Analysis will be performed including patients in the efficacy population with ICH bleeding. Mean, standard deviation, median, 95% CI for the median will be presented.

The NIHSS scores will be performed at baseline, at 1 hour after the end of the andexanet infusion, 12 hours after the end of the andexanet infusion and at Day 30 follow-up. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The patient total score will be analyzed as raw scores and as change from baseline. Analysis will include all patients in the efficacy population with ICH bleeding. Mean, standard deviation, median, 95% CI for the median will be presented.

Analyses will be presented for the overall population and by FXa inhibitor.

5.15.1.11. Other Analyses

In addition, other analyses will be performed, allowing for adjustment of potentially confounding variables. Variables that may confound evaluation of a correlation between reversal of anti-fXa activity with effective hemostasis include anatomical location of bleeding, mechanism of injury (e.g., blunt vs. penetrating trauma; traumatic vs. spontaneous), severity of injury, severity of bleeding, presence and timing of interventions to stop bleeding (e.g., endoscopic cautery of bleeding ulcers, surgical ligation of bleeding vessel), and use of coagulation or hemostatic factors. These analyses will be defined later in an addendum to this analysis plan and will be labeled as post hoc in the clinical study report.

5.16. Safety analysis

All safety analyses will be conducted using the Safety analysis population. Unless otherwise indicated, all analyses will be presented for an overall population (pooled across the different inhibitors) and stratified by the different inhibitors.

5.16.1. Extent of exposure

Drug exposure will be summarized by andexanet dose for the overall patient population and by FXa inhibitor, and by bleeding type. The number, percentage, exact 95% CI for percentage for the andexanet dose completed, modified, interrupted, and discontinued, and all treatment-emergent adverse events (TEAEs) that result on andexanet dose modification will be presented. In addition, the reason for drug modification, interruption, and discontinuation will be presented by patient as data listing.

In addition, patients that received re-dosing and the reason for re-dosing will be presented as data listing.

5.16.2. Adverse Events

A TEAE is defined as any AE that has an onset on or after the first dose of andexanet, or any pre-existing condition that has worsened on or after the first dose of andexanet. TEAEs will be attributed to andexanet using the following rules:

A treatment-related adverse event is defined as a TEAE possibly or probably related to andexanet. TEAEs with missing relationship will be counted as being treatment-related for analysis purposes.

The incidence of TEAEs, treatment-related AEs, TEAEs that led to early withdrawals, and serious AEs (SAEs) will also be summarized by maximum severity and most-related relationship to andexanet by MedDRA primary system organ class and preferred term. The summary will include the total number and percentage of patients reporting a particular event. In counting the number of events reported, a continuous event, i.e. reported more than once and which did not cease, will be counted only once; non-continuous adverse events reported several times by the

same patient will be counted as multiple events. AEs occurring prior to andexanet treatment will be listed separately. Adverse events will be coded using MedDRA version 18.0.

Narratives of deaths, serious and other significant adverse events will be provided in the relevant section of the study report.

A complete patient listing of all adverse events will be provided in Appendix 16.2 to the study report. This listing will include treatment, AE verbatim, MedDRA primary system organ class and preferred term, the day of onset and cessation of event relative to first dosing of andexanet, duration of AE, whether serious (yes/no), severity, relationship to andexanet, action taken and outcome, treatment emergent and non-treatment emergent events will be listed separately.

AEs of special interest will be summarized. As defined in the protocol, AEs of special interest are thrombotic or embolic events of any severity, whether serious or not, and infusion reactions that are either serious or severe or both.

Adverse events will be summarized for the following subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age deciles, and FXa inhibitor.

5.16.3. Deaths

All deaths will be assessed, and the causes of death adjudicated, by the EAC. Deaths due to cardiovascular causes (i.e., resulting from MI, sudden cardiac death, heart failure, stroke, CV procedures, CV hemorrhage, and other CV causes) will be classified as related to bleeding or non-hemorrhagic.

Kaplan-Meier curve for time to death will be presented by treatment by FXa inhibitor, andexanet dose, and andexanet manufacturing process. Patients who discontinue the study prior to Day 30 with an unknown survival assessment will be censored at the time of the last visit. Also, patients that completed the study (i.e., Day 30) will be censored at Day 30.

In addition, the proportion of patients that died during the 30 day follow-up with exact 95% CI will be presented for the overall safety population, by age category, region, FXa inhibitor, bleeding type, andexanet dose, andexanet manufacturing process, and by age deciles. In addition, the cause of death will be summarized.

The relationship between anti-fXa and 30-day mortality, will be analyzed (in the safety population), using a logistic regression model, with Age included as a covariate.

- 30-day mortality will define Death as Death at any time (including deaths recorded after Day 30). A sensitivity analysis defining Death as above (died during the 30 day follow-up) will be performed as well.
- Age will be entered into the model using a cubic spline transformation to best reflect the relationship with mortality.

- The Full Model will be compared to the Reduced Model with a Likelihood Ratio Test. The Reduced Model will be rejected in favor of the Full Model if the Likelihood Ratio Test p-value is <0.05.
    - Reduced Model: includes Age (with cubic spline transformation)
    - Full Model: includes Age (with cubic spline transformation) and an indicator variable for anti-fXa at on-treatment Nadir < threshold (where the threshold is 30 ng/mL for the DOACs, and 0.10 IU/mL for Enoxaparin).
- The area under the receiver operating characteristic (AUC under ROC) with the 95% CI will be presented for the Full Model.
- Descriptive statistics, odds ratios with the corresponding 95% confidence intervals, and p-values from the models will be presented also.

5.16.4. Thrombotic Events

Potential Thrombotic Events (TEs) will be submitted by each Investigator for adjudication by the EAC using definitions pre-specified in the EAC Charter. The proportion of patients in the safety population who are adjudicated to have a TE by the independent EAC will be summarized. An exact 95% CI will be reported. Analysis will be performed for the safety patient population, by age category, sex, region, FXa inhibitor, bleeding type, andexanet dose, andexanet manufacturing process, medical history (i.e., atrial fibrillation (AF), Ischemic Stroke or Transient Ischemic Attack (CVA/TIA), Venous Thrombotic Event (VTE), or Cancer); and the type of TE (i.e., Ischemic Stroke (CVA), Myocardial Infarction (MI), Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE), Arterial Systemic Embolism (ASE), and Transient Ischemic Attack (TIA).Also, the age, sex, FXa inhibitor, type of bleeding, previous history of TE, hospital length of stay and deaths for patients with and without thrombotic events will be compared.

An additional summary of possible TEs will be presented using a broader definition of TEs as recommended by FDA. See Section 4.6.8 for further details on the selection of events. The proportion of patients in the safety population who have a TE by this broader definition will be summarized. An exact 95% CI will be reported.

5.16.5. Antibodies to Andexanet, FX, FXa, HCP

To measure anti-andexanet antibodies (i.e., anti-drug antibodies [ADA]), samples are tested up to 3 times, each using a different electrochemiluminescence assay. The samples are tested sequentially so only samples that are positive in the previous assay are progressed to the next assay:

First, a screening assay is used to determine if there is antibody present in the sample. The result of this assay is either Detected or Not Detected.

Second, only if a sample has Detected antibody from the screening assay, a confirmatory assay is used to determine if the antibody is specific for the drug. The result of this assay is either Confirmed or Not Confirmed, and is only reported for samples for which the screening assay result was detected.

Third, if a sample has been confirmed to have ADA from the Confirmatory Assay, a titer assay is used to further determine the magnitude of the response. The titer result is a numeric value which is the reciprocal of the last dilution above the cut point that is positive.

The nature of any confirmed ADA will be further evaluated by a Neutralizing Antibody Activity assay. This assay uses the same Anti-fXa Activity assay for the PD samples, except that to each neutralizing antibody sample is added, *ex vivo*, a known amount of the anticoagulant (e.g., rivaroxaban), or anticoagulant *plus* andexanet. Each sample will have two test results listed as "Anticoagulant" and "Anticoagulant+andexanet." The neutralizing activity of the antibodies in the sample is inferred from the anti-fXa activity change from Pre-dose baseline to the later time points with the addition of anticoagulant vs. anticoagulant *plus* andexanet.

In data listings, the final result of the Anti-fXa activity assay will be reported as one of the following:

- Not Detected, if the Screening Assay is negative
- Not Confirmed, if the Screening Assay is positive but the Confirmatory Assay is negative
- Numeric, if the Screening Assay and Confirmatory Assay are both positive
- Neutralizing numeric, only for ADA, and only if the Screening Assay and Confirmatory Assay are both positive

In addition to the above, a modified Bethesda assay will be used to assess the potential presence of neutralizing antibodies against endogenous FX/FXa in all plasma samples from patients enrolled following the implementation of Protocol Amendment 4. The results will be listed by patient.

5.16.6. Clinical Laboratory Evaluations

Descriptive statistics will be calculated for the changes from baseline in hematology at 12 hours post andexanet dosing.

Each measurement will be classed as below, within, or above normal range, based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from screening to end of study follow-up visit will be presented.

5.16.7. Vital and Hemodynamic Compromise Signs

Summary statistics for observed and changes from baseline in systolic and diastolic blood pressure, pulse rate, and heart rate will be tabulated at 1, 4, 8 and 12 hours post-dose.

24 hour vital sign data was only collected prior to issuing of protocol amendment 2 and therefore will be listed in Appendix but not formally summarized.

Threshold-based outlier analyses of post-dosing vital sign data will be presented based on the following definitions:

- Systolic blood pressure < 70 mmHg or > 180 mmHg
- Diastolic blood pressure < 40 mmHg or > 120 mmHg
- Pulse rate < 40 bpm or > 160 bpm
- Respiratory rate < 12 or > 40 breath/min

Details of whether the subjects showed any signs of post-baseline hemodynamic compromise will not be formally tabulated but listed in Appendix 16.2.

5.16.8. Post Dose Procedures Performed to Evaluate Bleeding

Number of patients who had the evaluative diagnostic, therapeutic and imaging procedures used after the first andexanet dose along with the procedures used will be tabulated Change to Original Protocol and Planned Statistical Analysis

5.17. Changes to the Original Protocol and Planned Statistical Analysis

5.17.1. Protocol Amendments

No patients were enrolled under the original protocol (dated 30 July 2014). For the current dataset, all patients were enrolled under one of four protocol amendments: Protocol Amendment 1, dated 30 January 2015; Protocol Amendment 2 dated 07 May 2015; Protocol Amendment 3, dated 27 October 2015 (a Netherlands-specific amendment); Protocol Amendment 4, dated 06 January 2017, Protocol Amendment 5, dated 02 July 2018, and Protocol Amendment 6, dated 30 November 2018.

Changes in the protocol that impacted the conduct of the study included the following:

5.17.1.1. Amendment 1 (30 January 2015)

- Modified the primary efficacy objective and primary efficacy endpoint to include changes in anti-fXa activity. The two primary efficacy endpoints will be tested sequentially, with the proportion achieving hemostatic efficacy tested only if the change in anti-fXa activity is first demonstrated.
- Modified the secondary efficacy objective and secondary efficacy endpoint to assess the relationship between the two primary efficacy endpoints: to evaluate the relationship between change from baseline to the evaluation period in anti-fXa activity and effective hemostasis.

- Eliminated the original Study Day 1, 24-hour study data point and updated time points to Day 1, 8-hour and Day 1, 12-hour data points.
- Clarified the requirements, inclusion, and exclusion criteria regarding acute major bleeding.
- Changed the definition of history prior to screening from 1 month to 2 weeks.
- Modified follow-up to include rescue therapy for patients with a poor or no response.
- Provided specific detail on the measurement of closed bleeds to document hemostatic control.
- Increased the number of sites allowed in North America and Europe from 60 to 120.

5.17.1.2. Amendment 2 (07 May 2015)

- Modified the duration of safety follow up from 45 to 30 days to align follow-up period with standard clinical practice for ICH recovery timelines.
- Clarified that (visible) bleeding must be overt to qualify for inclusion in this trial.
- Clarified that ICH bleeds can be diagnosed and assessed with either CT or MRI.
- Included edoxaban as one of the factor Xa inhibitors that could qualify a patient for this trial. Also, clarified that the list of factor Xa inhibitors being studied in this study is restricted to apixaban, edoxaban, rivaroxaban, and enoxaparin.
- Clarified that patients who are scheduled for surgery to occur within the first 12 hours after receiving andexanet should not be enrolled in this study.
- Clarified the blood and blood-related products allowed as well as the time frames allowed.
- Increased the size of allowable hematoma volume from 30 cc to 60 cc to enable the patient population to be more representative of what might be expected in the clinical setting.
- Shortened and/or consolidated the restrictions around duration of prior exposure to medications to within 7 days of andexanet treatment, based on expected duration of effect.
- Provided specificity around rating of hemostatic efficacy for different subtypes of ICH.

5.17.1.3. Amendment 3 (27 October 2015)

Amendment 3 was a country-specific amendment for the Netherlands. The content of Amendment 3 was largely identical to that of Amendment 2, with the exception that the discretion to enroll patients who were unable to provide informed consent for themselves, either by proxy or emergency consent, was dependent on local laws and regulations.

5.17.1.4. Amendment 4 (06 January 2017)

- Increased sample size from 250 patients to 350 patients.
- Enriched patient population for ICH; ensured a minimum of 110 efficacy evaluable ICH patients, including 50 patients at high risk for hematoma expansion.
- Added a requirement for a reasonable expectation that a patient would be treated with andexanet within 2 hours after a baseline scan (ICH patients only).
- Excluded patients with visible, intra-articular, and musculoskeletal bleeding.
- Excluded patients for whom the Investigator believed that the hemoglobin would drop below 8 g/dL after volume resuscitation.
- Changed threshold of efficacy evaluability for enoxaparin patients from 0.5 IU/mL to 0.25 IU/mL.
- Added clinical criteria for re-bleeding and guidance for re-dosing of andexanet in the event of re-bleeding.
- Added re-bleeding, TFPI, ATIII, anti-IIa activity, GCS, mRS, and NIHSS as exploratory efficacy endpoints.
- Converted thrombin generation from a safety endpoint to an efficacy endpoint, and mortality from an efficacy endpoint to a safety endpoint.
- Updated andexanet dosing recommendations.

5.17.1.5. Amendment 5 (02 July 2018)

- To established lower anti-fXa activity threshold for patients taking edoxaban to reflect contemporary understanding of risks and benefits of edoxaban.
- Efficacy evaluable patients was re-defined as follows: All patients must have a central laboratory-determined anti-fXa activity $\geq$ 75 ng/mL for patients receiving apixaban and rivaroxaban, $\geq$ 40 ng/mL for patients receiving edoxaban, and $\geq$ 0.25 IU/mL for patients receiving enoxaparin. All other criteria stayed the same.
- Exclusion criteria #5 was updated as follows: The patient has a recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) as follows: Venous Thromboembolism (VTE; e.g., deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis), myocardial infarction (including an isolated troponin elevation), disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening (see Appendix E for DIC scoring algorithm).
- Clarified definition of re-bleeding to be consistent throughout protocol.
- Update and clarification for IP return and destruction.

5.17.1.6. Amendment 6 (30 November 2018).

- Corrected an error in the Synopsis and updated for accuracy and to align with the protocol body.
- Clarified that adverse events *and survival* was to be followed through the study.
- Updated to simplify the description of the study periods related to safety monitoring.
- As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of FXa inhibitor within 18 hours, if the timing is known. (If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible–following signing of the ICF and completion of pretreatment procedures–but no later than 3 hours following signing of the ICF.)
- Updated for clarity exclusion criteria 4.2.
- Updated the andexanet dosing to reflect accurate ranges of < 30 mg (low dose) and ≥ 30 mg (high dose) for andexanet dosing in patients receiving edoxaban.

5.17.2. Changes to the Analysis Plan

This analysis plan is an update to version 3.0 (09 August 2019). The main changes to version 3.0 of the Statistical Analysis Plan are:

1) Remove stratification of Generation 1 and 2 from all analyses
2) Include an extra definition and summary of Thrombotic Events using a broader list of preferred terms, per FDA request
3) Reclassify Urinary Bleeds from the "GI" category to the "Other" category
4) Pre-specify an analysis of the
    a. correlation between reversal of anti-fXa activity with effective hemostasis, and
    b. correlation between reversal of anti-fXa activity with mortality

Previous Changes to SAP

The previous analysis plan was an update to versions 1.0 (30 October 2018) and 2.0 (21 November 2018). The main purpose of changes to the versions 1.0 and 2.0 of the Statistical Analysis Plan was to accommodate additional patients treated with edoxaban and patients in Japan, and to align the SAP with the last version of the protocol (i.e., amendment 5 and 6).

The main change to the SAP (as in the protocol) regards the definition of efficacy evaluable patient population to include requirement of a minimum anti-fXa activity level for edoxaban as follows:

The Efficacy Population will include all patients in the Safety Population who meet all of the following criteria:

- Are determined by the EAC to meet the clinical bleeding inclusion criteria.
- Have a baseline anti-fXa level
- Baseline anti-fXa level of at least 75 ng/mL for apixaban and rivaroxaban, **40 ng/mL for edoxaban**, or 0.25 IU/mL for patients receiving enoxaparin.

6.0 REFERENCES

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7.0 LIST OF TABLES

Sample tables listed below. These will not be updated with changes.

Table Number	Table Title
Table 14.1.1.1	Table 14.1.1.1 Patient Enrollment by Protocol Version (Safety Population)
Table 14.1.1.2	Table 14.1.1.2. Baseline Characteristics (Safety and Efficacy Population)
Table 14.1.1.3a	Table 14.1.1.3a. Baseline Characteristics by Generation (Safety Population)
Table 14.1.1.3b	Table 14.1.1.3b. Baseline Characteristics by Generation (Efficacy Population)
Table 14.1.1.3c	Table 14.1.1.3c. Baseline Characteristics by Region (Safety Population)
Table 14.1.1.3d	Table 14.1.1.3d. Baseline Characteristics by Region (Efficacy Population
Table 14.1.1.4	Table 14.1.1.4. Medical History by Andexanet Generation (Safety Population)
Table 14.1.1.5	Table 14.1.1.5. Medical History by Region (Safety Population)
Table 14.1.1.6	Table 14.1.1.6. Details of Hospitalization (Safety and Efficacy Populations)
Table 14.1.1.7	Table 14.1.1.7. Anti-platelet & NSAID Agents Administered Prior to Andexanet Treatment
Table 14.1.1.8	Table 14.1.1.8. Hemoglobin Over Time (Safety Population)
Table 14.1.1.9	Table 14.1.1.9 Baseline Cockcroft-Gault Creatinine Clearance (Safety and Efficacy Populations)
Table 14.1.1.10	Table 14.1.1.10. Baseline Characteristics of Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate Over Time by Bleed Type (Safety Population)
Table 14.1.1.11	Table 14.1.1.11. Hemodynamic Compromise Signs at 3 Hours Before Bolus & 15 Minutes Before Bolus (Safety Population)
Table 14.1.1.12a	Table 14.1.1.12a. Baseline Prognostic Clinical Indicators in Patients with ICH by Region (Safety Population)
Table 14.1.1.12b	Table 14.1.1.12b. Baseline Prognostic Clinical Indicators in Patients with ICH by Region (Efficacy Population)
Table 14.1.1.12c	Table 14.1.1.12c. Baseline Prognostic Clinical Indicators in Patients with ICH by Generation (Safety Population)
Table 14.1.1.12d	Table 14.1.1.12d. Baseline Prognostic Clinical Indicators in Patients with ICH by Generation (Efficacy Population)
Table 14.1.1.12e	Table 14.1.1.12e. Baseline Prognostic Clinical Indicators in Patients with ICH (Safety & Efficacy Population)
Table 14.1.1.13a	Table 14.1.1.13a. Summary of Patients Enrolled by FXa Inhibitor and Primary Bleed Type (Safety Population)
Table 14.1.1.13b	Table 14.1.1.13b. Summary of Patients Enrolled by Age Group and Primary Bleed Type (Safety Population)
Table 14.1.1.14	Table 14.1.1.14. Time (Hours) from the last dose of FXa Inhibitor to Start of Andexanet Treatment (Safety Population)
Table 14.1.1.15	Table 14.1.1.15. Pre-dose Treatment of Bleeding Episode by Region (Safety Population)
Table 14.1.1.16	Table 14.1.1.16. Coagulation and Biochemistry at 3 Hours Before Bolus (Safety Population)
Table 14.1.1.17	Table 14.1.1.17. Baseline Anatomic Characteristics of Intracranial Hemorrhage by Bleeding Compartment (Safety and Efficacy Population)

Table Number	Table Title
Table 14.2.1.1a	Table 14.2.1.1a. Summary for Anti-fXa Activity by FXa Inhibitor (Efficacy Population)
Table 14.2.1.1b	Table 14.2.1.1b. Summary for Anti-fXa Activity by FXa Inhibitor (Safety Population)
Table 14.2.1.2a	Table 14.2.1.2a. Summary for Anti-fXa Activity (ng/mL) for Patients who Received Apixaban (Efficacy Population)
Table 14.2.1.2b	Table 14.2.1.2b. Summary for Anti-fXa Activity (ng/mL) for Patients who Received Rivaroxaban (Efficacy Population)
Table 14.2.1.2c	Table 14.2.1.2c. Summary for Anti-fXa Activity (ng/mL) for Patients who Received Enoxaparin (Efficacy Population)
Table 14.2.1.2d	Table 14.2.1.2d. Summary for Anti-fXa Activity (ng/mL) for Patients who Received Edoxaban (Efficacy Population)
Table 14.2.1.3	Table 14.2.1.3. Summary for Anti-fXa Activity for patients with Supratherapeutic Values by FXa Inhibitor (Efficacy Population)
Table 14.2.1.4	Table 14.2.1.4. Patients with Baseline Anti-fXa Activity of Apixaban >300 ng/mL and of Rivaroxaban >210 or >400 ng/mL (Low and High Andexanet Doses) (Efficacy Population)
Table 14.2.1.5	Table 14.2.1.5. Summary of Baseline Anti-fXa Activity of Apixaban >300 ng/mL and of Rivaroxaban >210 or >400 ng/mL (Low and High Andexanet Doses) (Efficacy Population)
Table 14.2.1.6a	Table 14.2.1.6a. Summary for Anti-fXa Activity (ng/mL) for Patients who Received Apixaban by Generation (Efficacy Population)
Table 14.2.1.6b	Table 14.2.1.6b. Summary for Anti-fXa Activity (ng/mL) for Patients who received Rivaroxaban by Generation (Efficacy Population)
Table 14.2.1.6c	Table 14.2.1.6c. Summary for Anti-fXa Activity (ng/mL) for Patients who received Edoxaban by Generation (Efficacy Population)
Table 14.2.1.6d	Table 14.2.1.6d. Summary for Anti-fXa Activity (IU/mL) for Patients who received Enoxaparin by Generation (Efficacy Population)
Table 14.2.2.1a	Table 14.2.2.1a. Hemostatic Efficacy at 12 Hours Post Andexanet (Efficacy Population)
Table 14.2.2.1b	Table 14.2.2.1b. Hemostatic Efficacy at 12 Hours Post Andexanet (Safety Population)
Table 14.2.2.1c	Table 14.2.2.1c. Analyses of Hemostatic Efficacy at 12 Hours Post Andexanet (Efficacy Population)
Table 14.2.2.2	Table 14.2.2.2. Hemostatic Efficacy at 12 Hours Post Andexanet by Subgroup (Efficacy Population)
Table 14.2.2.3	Table 14.2.2.3. Hemostatic Efficacy by Andexanet Generation
Table 14.2.2.4	Table 14.2.2.4. Anti-fXa Activity by Hemostatic Efficacy (Efficacy Population)
Table 14.2.2.5a	Table 14.2.2.5a. Hemostatic Efficacy at 12 Hours Post Andexanet by Baseline Anti-fXa Activity of Apixaban and Rivaroxaban (Safety Population)
Table 14.2.2.5b	Table 14.2.2.5b. Hemostatic Efficacy at 12 Hours Post Andexanet by Baseline Anti-fXa Activity of Enoxaparin (Safety Population)

Table Number	Table Title
Table 14.2.2.5c	Table 14.2.2.5c. Hemostatic Efficacy at 12 Hours Post Andexanet by Baseline Anti-fXa Activity of Edoxaban (Safety Population)
Table 14.2.2.6	Table 14.2.2.6. Distribution of Excellent, Good, and Poor/None Hemostatic Efficacy by FXa Inhibitor and Percentage Reduction in Anti-fXa Activity (Efficacy Population)
Table 14.2.2.7	Table 14.2.2.7. Summary of Possible Confounders Between Anti-fXa Activity and Hemostatic Efficacy (Efficacy Population)
Table 14.2.2.8	Table 14.2.2.8. Distribution of Excellent, Good, and Poor/None Hemostatic Efficacy at 12 Hours Post Andexanet by Subgroup (Efficacy Population)
Table 14.2.2.9	Table 14.2.2.9. Hemostatic Efficacy of Evaluable or non-Evaluable Patients at 12 Hours Post Andexanet (Efficacy Population)
Table 14.2.3.1a	Table 14.2.3.1a. Relationship between Anti-fXa Activity and Hemostatic Efficacy for Patients who Received Apixaban or Rivaroxaban
Table 14.2.3.1b	Table 14.2.3.1b. Odds Ratio for Anti-fXa Activity and Hemostatic Efficacy for Patients who Received Apixaban or Rivaroxaban
Table 14.2.3.2a	Table 14.2.3.2a. Relationship between Anti-fXa Activity and Hemostatic Efficacy for Patients with ICH who Received Apixaban or Rivaroxaban
Table 14.2.3.2b	Table 14.2.3.2b. Odds Ratio for Anti-fXa Activity and Hemostatic Efficacy for Patients with ICH who Received Apixaban or Rivaroxaban
Table 14.2.3.5	Table 14.2.3.5. Effect of Baseline Characteristics on the Relationship between Anti-fXa Activity and Hemostatic Efficacy in Patients with ICH (Apixaban and Rivaroxaban)
Table 14.2.4.1a	Table 14.2.4.1a. Free (Unbound) Plasma Concentration (ng/mL) Over Time of Apixaban (Efficacy Population)
Table 14.2.4.1b	Table 14.2.4.1b. Free (Unbound) Plasma Concentration (ng/mL) Over Time of Rivaroxaban (Efficacy Population)
Table 14.2.4.1c	Table 14.2.4.1c. Free (Unbound) Plasma Concentration (ng/mL) Over Time of Edoxaban (Efficacy Population)
Table 14.2.4.2a	Table 14.2.4.2a. Endogenous Thrombin Potential & Non TF Endogenous Thrombin Potential (Efficacy Population)
Table 14.2.4.2b	Table 14.2.4.2b. Endogenous Thrombin Potential & Non TF Endogenous Thrombin Potential Over Time (Efficacy Population)
Table 14.2.4.2c	Table 14.2.4.2c. Endogenous Thrombin Potential Parameters (Efficacy Population)
Table 14.2.4.2d	Table 14.2.4.2d. Non-TF Endogenous Thrombin Potential Parameters (Efficacy Population)
Table 14.2.4.2e	Table 14.2.4.2e. Endogenous Thrombin Potential by FXa Inhibitor Over Time (Efficacy Population)
Table 14.2.4.3a	Table 14.2.4.3a. Tissue Factor Pathway Inhibitor (TFPI) Over Time (Safety Population)
Table 14.2.4.3b	Table 14.2.4.3b. Tissue Factor Pathway Inhibitor (TFPI) Over Time (Efficacy Population)
Table 14.2.4.4	Table 14.2.4.4. Antithrombin III (ATIII) Over Time (Efficacy Population)

Table Number	Table Title
Table 14.2.4.5	Table 14.2.4.5. Anti-factor IIa Activity (ANTI-IIA, IU/mL) Over Time of Enoxaparin Patients (Safety Population)
Table 14.2.4.6	Table 14.2.4.6. Hemostatic Efficacy of Patients with ICH at 12 Hours Post Andexanet (Efficacy Population)
Table 14.2.4.7a	Table 14.2.4.7a. Proportion of Patients Received Red Blood Cell Transfusion Post Andexanet (Efficacy Population)
Table 14.2.4.7b	Table 14.2.4.7b. Proportion of Patients Received Red Blood Cell Transfusion Post Andexanet (Safety Population)
Table 14.2.4.8a	Table 14.2.4.8a. Clinical Neurologic Status (Modified Rankin Score [mRS]) for Patients with ICH (Efficacy Population)
Table 14.2.4.8b	Table 14.2.4.8b. Clinical Neurologic Status (Glasgow Coma Scale & National Institutes of Health Stroke Scale) for Patients with ICH (Efficacy Population)
Table 14.3.1.1	Table 14.3.1.1. Summary of Adverse Events (Safety Population)
Table 14.3.1.2	Table 14.3.1.2. Summary of Adverse Events by Andexanet Generation (Safety Population)
Table 14.3.1.3a1	Table 14.3.1.3a1. Most Common ≥ 10% TEAE by MedDRA Primary System Organ Class (Safety Population)
Table 14.3.1.3a2	Table 14.3.1.3a2. Most Common ≥ 3% TEAE by Preferred Term (Safety Population)
Table 14.3.1.3b1	Table 14.3.1.3b1. TEAE by MedDRA Primary System Organ Class, Andexanet Generation, and Severity (Safety Population)
Table 14.3.1.3b2	Table 14.3.1.3b2. TEAE by MedDRA Preferred Term, Andexanet Generation, and Severity (Safety Population)
Table 14.3.1.3c	Table 14.3.1.3c. TEAE by FXa Inhibitor, MedDRA Primary System Organ Class, Preferred Term, and Andexanet Generation (Safety Population)
Table 14.3.1.3d	Table 14.3.1.3d. TEAE by Age, MedDRA Primary System Organ Class, Preferred Term, and Andexanet Generation (Safety Population)
Table 14.3.1.3e	Table 14.3.1.3e. TEAE by Sex, MedDRA Primary System Organ Class, Preferred Term, and Andexanet Generation (Safety Population)
Table 14.3.1.3f	Table 14.3.1.3f. TEAE by Race, MedDRA Primary System Organ Class, Preferred Term, and Andexanet Generation (Safety Population)
Table 14.3.1.3g	Table 14.3.1.3g. TEAE by MedDRA Preferred Term (Safety Population)
Table 14.3.1.4a	Table 14.3.1.4a. TEAE Overview by FXa Inhibitor (Safety Population)
Table 14.3.1.4b	Table 14.3.1.4b. TEAE Overview by Age Category (Safety Population)
Table 14.3.1.4c	Table 14.3.1.4c. TEAE Overview by Sex (Safety Population)
Table 14.3.1.4d	Table 14.3.1.4d. TEAE Overview by Race (Safety Population)
Table 14.3.1.4e	Table 14.3.1.4e. TEAE by Severity and Age (Safety Population)
Table 14.3.1.4f	Table 14.3.1.4f. TEAE by Severity and Sex (Safety Population)
Table 14.3.1.4g	Table 14.3.1.4g. TEAE by Severity and Race (Safety Population)
Table 14.3.1.4h	Table 14.3.1.4h. Number of Patients with TEAEs by Age (Safety Population)

Table Number	Table Title
Table 14.3.1.4i	Table 14.3.1.4i. Number of Patients with TEAEs by Sex (Safety Population)
Table 14.3.1.4j	Table 14.3.1.4j. Number of Patients with TEAEs by Race (Safety Population)
Table 14.3.1.5a	Table 14.3.1.5a. Treatment Related TEAE by MedDRA Preferred Term (Safety Population)
Table 14.3.1.5b	Table 14.3.1.5b. Treatment Related TEAE by FXa Inhibitor (Safety Population)
Table 14.3.1.5c	Table 14.3.1.5c. Treatment Related TEAE by Age (Safety Population)
Table 14.3.1.5d	Table 14.3.1.5d. Treatment Related TEAE by Sex (Safety Population)
Table 14.3.1.5e	Table 14.3.1.5e. Treatment Related TEAE by Race (Safety Population)
Table 14.3.1.5f	Table 14.3.1.5f. Time (days) of Treatment Related TEAE by FXa Inhibitor (Safety Population)
Table 14.3.1a	Table 14.3.1a. Study Drug Exposure (Safety & Efficacy Population)
Table 14.3.1b	Table 14.3.1b. Study Drug Exposure by Generation (Safety Population)
Table 14.3.1c	Table 14.3.1c. Study Drug Exposure by FXa Inhibitor (Safety Population)
Table 14.3.1d	Table 14.3.1d. Study Drug Exposure by Bleed Type (Safety Population)
Table 14.3.2.1a	Table 14.3.2.1a. Adjudicated Reason of Deaths (Safety Population)
Table 14.3.2.1b	Table 14.3.2.1b. Demographics of Patients Who Died (Safety Population)
Table 14.3.2.1c	Table 14.3.2.1c. Number of Thrombotic Events and Deaths Before Hospital Discharge (Safety Population)
Table 14.3.2.2	Table 14.3.2.2. Number of Deaths by Bleed Type, FXa Inhibitor, and Andexanet Generation (Safety Population)
Table 14.3.2.3	Table 14.3.2.3. Mortality Rates Stratified by Age Decile (Safety Population)
Table 14.3.2.4	Table 14.3.2.4. Age of Patients Who Died by Andexanet Generation (Safety Population)
Table 14.3.2.5	Table 14.3.2.5. Time to Death (Days) by Generation with FXa Inhibitor (Safety Population)
Table 14.3.2.7a	Table 14.3.2.7a. TE-SAE by MedDRA Primary System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.7b	Table 14.3.2.7b. TE-SAE Considered Possibly or Probably Related to Andexanet Treatment (Safety Population)
Table 14.3.2.7c	Table 14.3.2.7c. TE-SAE by FXa Inhibitor (Safety Population)
Table 14.3.2.7d	Table 14.3.2.7d. TE-SAE by Age (Safety Population)
Table 14.3.2.7e	Table 14.3.2.7e. TE-SAE by Sex (Safety Population)
Table 14.3.2.7f	Table 14.3.2.7f. TE-SAE by Race (Safety Population)
Table 14.3.2.9	Table 14.3.2.9. Characteristics of Thrombotic Events Stratified by TE Type[1] (Safety Population)
Table 14.3.2.10	Table 14.3.2.10. Comparison of Thrombotic Events vs. No Events Stratified by Bleed Type (Safety Population)
Table 14.3.2.11	Table 14.3.2.11. Comparison of Patients with Thrombotic Events vs. Patients Without Thrombotic Events (Safety Population)

Table Number	Table Title
Table 14.3.2.12	Table 14.3.2.12. Characteristics of Thrombotic Events and Re-anticoagulation Stratified by Generation and Bleed Type (Safety Population)
Table 14.3.2.13	Table 14.3.2.13. Thrombotic Events and Re-anticoagulation (Safety Population)
Table 14.3.2.14	Table 14.3.2.14. Thrombotic Events (Safety Population)
Table 14.3.2.15a	Table 14.3.2.15a. Analysis of Hematoma Expansion in Patients with Intraparenchymal Volume (mL) (Safety Population)
Table 14.3.2.15b	Table 14.3.2.15b. Analysis of Hematoma Expansion in Patients with Intraparenchymal Volume (mL) (Efficacy Population)
Table 14.3.4.1	Table 14.3.4.1. Antibodies to Andexanet, FX, FXa (Safety Population)
Table 14.3.4.2a	Table 14.3.4.2a. Systolic Blood Pressure and Diastolic Blood Pressure Over Time After Andexanet Treatment by Bleed Type (Safety Population)
Table 14.3.4.2b	Table 14.3.4.2b. Heart Rate and Respiratory Rate Over Time After Andexanet Treatment by Bleed Type (Safety Population)
Table 14.3.4.3	Table 14.3.4.3. Baseline and Change from Baseline in Hemoglobin at 12 hours Post Andexanet Treatment (Safety Population)

8.0 LIST OF FIGURES

9.0 LIST OF LISTINGS (NOTE THIS MAY BE MODIFIED)

Listing No	Listing Title
Listing 16.1.6	Listing 16.1.6. Lot Numbers at Baseline
Listing 16.2.1.1	Listing 16.2.1.1. Patient Disposition (Safety Population)
Listing 16.2.2.2	Listing 16.2.2.2. Protocol Deviations: Fail to Meet Exclusion Criteria (Safety Population)
Listing 16.2.3.1	Listing 16.2.3.1. Patients Excluded from the Efficacy Population (Safety Population)
Listing 16.2.4.1	Listing 16.2.4.1. Baseline Characteristics (Safety Population)
Listing 16.2.4.2	Listing 16.2.4.2. Demographics (Safety Population)
Listing 16.2.4.3	Listing 16.2.4.3. FXa Inhibitor Treatment (Safety Population)
Listing 16.2.4.4	Listing 16.2.4.4. Hematology (Hematocrit and Platelet Count) within 3 Hours and within 15 Minutes before Bolus (Safety Population)
Listing 16.2.4.5	Listing 16.2.4.5. Coagulation and Biochemistry within 3 Hours before Bolus (Safety Population)
Listing 16.2.4.6	Listing 16.2.4.6. Medical History (Safety Population)
Listing 16.2.4.7	Listing 16.2.4.7. Medication Within 7 Days Prior to Screening (Safety Population)
Listing 16.2.4.8	Listing 16.2.4.8. Details of Hospitalization (Safety Population)
Listing 16.2.4.9	Listing 16.2.4.9. Vital and Hemodynamic Compromise Signs (Safety Population)
Listing 16.2.5.1	Listing 16.2.5.1. Study Drug Exposure Comments (Safety Population)
Listing 16.2.5.2	Listing 16.2.5.2. Andexanet IV Bolus or Infusion Dose Modification (Safety Population)
Listing 16.2.5.3	Listing 16.2.5.3. Patients That Received Andexanet Treatment > 18 hours Post Last FXa Inhibitor Dose (Safety Population)
Listing 16.2.6.1	Listing 16.2.6.1. Anti-fXa Levels by Patient (Safety Population)
Listing 16.2.6.2	Listing 16.2.6.2. Listing for Primary Efficacy Outcomes - Percent Change in Anti-fXa Activity & Hemostatic Efficacy (Safety Population)
Listing 16.2.6.3	Listing 16.2.6.3. Endogenous Thrombin Potential Parameters (Efficacy Population)
Listing 16.2.6.4	Listing 16.2.6.4. Non TF Endogenous Thrombin Potential Parameters (Efficacy Population)
Listing 16.2.6.5	Listing 16.2.6.5. Use of Red Blood Cell Transfusion After Andexanet Treatment (Safety Population)
Listing 16.2.6.6	Listing 16.2.6.6. Use of Other Blood Products and Hemostatic Agents after Andexanet Treatment (Safety Population)
Listing 16.2.6.7	Listing 16.2.6.7. Free Fraction (Unbound) Plasma Concentration (ng/mL) over Time by FXa Inhibitor (Efficacy Population)
Listing 16.2.6.8	Listing 16.2.6.8. Thrombin Generation (Safety Population)
Listing 16.2.6.9	Listing 16.2.6.9. % Protein Binding over Time by FXa Inhibitor (Efficacy Population)

Listing No	Listing Title
Listing 16.2.6.10	Listing 16.2.6.10. Patients Receiving Post-Andexanet Coagulation factor Blood Products and Hemostatic Agents (Efficacy Population)
Listing 16.2.7.1	Listing 16.2.7.1. AEs Occurring Prior to Andexanet Treatment (Safety Population)
Listing 16.2.7.2	Listing 16.2.7.2. Listing of Treatment-Emergent Adverse Events (Safety Population)
Listing 16.2.7.3	Listing 16.2.7.3. Listing of Serious Adverse Events (Safety Population)
Listing 16.2.7.4	Listing 16.2.7.4. Listing of Treatment-Related Adverse Events (Safety Population)
Listing 16.2.7.5a	Listing 16.2.7.5a. Cause of Death Determined by Investigators (Safety Population)
Listing 16.2.7.5b	Listing 16.2.7.5b. Cause of Death Determined by Adjudication Committee (Safety Population)
Listing 16.2.7.6	Listing 16.2.7.6. Listing of Thrombotic Events (Safety Population)
Listing 16.2.7.7	Listing 16.2.7.7. Summary of Re-Bleeding and Re-dosing Andexanet (Safety Population)
Listing 16.2.7.8	Listing 16.2.7.8. Baseline ICH Score (Safety Population)
Listing 16.2.7.9	Listing 16.2.7.9. Listing for Reanticoagulation (Safety Population)
Listing 16.2.7.10	Listing 16.2.7.10. Listing of Coagulation Products used (Safety Population)
Listing 16.2.7.11	Listing 16.2.7.11. Listing of Hemostatic Treatment used (Safety Population)
Listing 16.2.7.12	Listing 16.2.7.12. Post-Treatment Use of Anti-Coagulation Medications (Safety Population)
Listing 16.2.7.13	Listing 16.2.7.13. Post-Treatment Use of Anti-Platelet Medications (Safety Population)
Listing 16.2.7.14	Listing 16.2.7.14. Infusion Reaction (Safety Population)
Listing 16.2.7.15	Listing 16.2.7.15. Initial Bleeding Assessment (Safety Population)
Listing 16.2.7.16	Listing 16.2.7.16. Visible Bleeding Assessment (Safety Population)
Listing 16.2.7.17	Listing 16.2.7.17. GI Bleeding Assessment (Safety Population)
Listing 16.2.7.18	Listing 16.2.7.18. Other Bleeding Assessment (Safety Population)
Listing 16.2.7.19	Listing 16.2.7.19. Intracranial Bleeding Assessment (Safety Population)
Listing 16.2.8.1	Listing 16.2.8.1. Antibodies to Andexanet, FX, FXa, HCP(Safety Population)
Listing 16.2.8.2	Listing 16.2.8.2. Patients at Day 30 or Day 45 Immunogenicity Sample (IS) (Safety Population)
Listing 16.2.8.3	Listing 16.2.8.3. Neutralizing Antibodies Against Endogenous FX/FXa (Safety Population)
Listing 16.2.8.4	Listing 16.2.8.4. Hematology (Hematocrit and Platelet Count) after Andexanet Treatment (Safety Population)