1. PROTOCOL OR AMENDMENT

- 19-515 Amendment 2.2 (Japan), Dated 30Aug2021
- 19-515 Amendment 2 (Global), Administrative Letter 2, Dated 25May2021
- 19-515 Amendment 2 (Global), Administrative Letter 1, Dated 01Apr2021
- 19-515 Amendment 2.1 (Japan), Dated 15Mar2021
- 19-515 Amendment 2 (Global), Dated 20Jul2020
- 19-515 Amendment 1 (Global), Dated 19Nov2019
- 19-515 Original Protocol (Global), Dated 16Sep2019

Protocol 19-515:

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO REQUIRE URGENT SURGERY (ANNEXA-S)

Protocol Amendment 2.2 (Japan)

MEDICAL MONITOR： PPD, MD
Medical Director
Alexion Pharmaceuticals, Inc.
Phone: PPD
Fax: PPD
email: PPD

PROTOCOL DATE：
Original: 16 September 2019
Amendment 1: 19 November 2019
Amendment 2: 20 July 2020
Amendment 2.1 (Japan): 15 March 2021
Amendment 2.2 (Japan): 30 AUG 2021

SPONSOR SIGNATORY：

PPD

01-Sep-2021 | 13:07:48 EDT

PPD, MD — DATE
Medical Director

INVESTIGATOR'S AGREEMENT

I have read the attached protocol amendment and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

_____

Signature of Principal Investigator

_____ _____

Name of Principal Investigator (Print) Date (DD Month YYYY)

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 2.2 (Japan) 30 AUG 2021

Overall Rationale for the Amendment:

Update necessitated from reconsideration of andexanet dosage in edoxaban 15-30 mg treated Japanese patients. High-dose andexanet will be administered to these patients.

Section # and Name	Description of Change	Brief Rationale
PROTOCOL SYNOPSIS Test Product, Dose, and Mode of Administration	Changed andexanet alfa dose in Edoxaban 15-30 mg treated patients. <Amendment 2.1 (Japan)> Last dose of FXa infibitor: < 8 hours - Edoxaban 15-30 mg (ONLY for VTE prophylaxis for patients undergoing orthopedic surgery of the lower limbs): **Low dose andexanet alfa** - Edoxaban 30 mg-60 mg: **High dose andexanet alfa** <Amendment 2.2 (Japan)> Last dose of FXa infibitor: < 8 hours - Edoxaban 15 mg-60 mg: **High dose andexanet alfa**	In study 16-508, there was no statistically significant difference in the reduction in anti-fXa activity between the andexanet low dose group and placebo group in healthy Japanese subjects who took 30 mg of edoxaban. Therefore, in edoxaban 15-30 mg treated patients, high-dose andexanet is considered to ensure the reversal effect without any specific risk. Thus, the andexanet dose changed to high dose.
6.2 Dosing and Administration Table 2	Same as above	Same as above
9.2.2. Assessment of Causal Relationship	Deleted.	Deleted due to the Administrative Change Letter on 01APR2021.

Amendment Rationale:

The amendment is prepared for executing the study under the regulatory requirements and medical practice in Japan. This country-specific amendment changed a part of the protocol contents and applies to all subjects enrolled in Japan.

Changes to the Protocol:

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Note: Enoxaparin is out of scope in Japan.

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25 May 2021

Protocol: 19-515 Protocol Amendment #2: 20 July 2020

Administrative Change Letter #2

Reason for Letter: Provide clarification on the appropriate delegation of Investigator responsibilities and exploratory endpoint

To those sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative update to the above referenced protocol version.

Clarification: Assessment of hemostatic efficacy
The current protocol states that the surgeon is responsible for determining the achievement of hemostatic efficacy according to the intraoperative hemostasis categories provided in Table 3 of Section 11.5.1. This administrative change letter serves to inform the study sites that the investigator (Principal investigator or sub-investigator as listed on the site delegation log) will be responsible for evaluating the endpoint of hemostatic efficacy. The investigator will consult with the research team and surgical team, if applicable, and will be responsible for interpretation of the endpoint prior to completing the hemostatic efficacy form. The investigator will also assess adverse events and provide oversight for study drug administration and monitoring of patients according to the protocol.

The attached hemostatic efficacy form has to be filled in for all patients which will serve a source document and also be provided to endpoint adjudication committee.

Rationale: Investigators have the required protocol and Good Clinical Practice training to participate in the evaluation of hemostatic efficacy, oversight of study drug administration, and assessment and monitoring of adverse events.

Clarification: Exploratory Endpoint
The current protocol incorrectly states that the endpoint of "Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and Hemostasis (ISTH) criteria" should be assessed "within 12 hours after the end of the initial surgery." This endpoint will be changed to read as follows: "Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and hemostasis (ISTH) criteria within 12 hours after the start of the initial surgery."

Rationale: There is a typo in the main body of current protocol (section 11.5.2.3) for this endpoint. The wording of the endpoint will be changed to be consistent with protocol synopsis for this endpoint.

If there any questions concerning these changes, please contact us. These changes will also be captured in any future protocol amendment.

PPD

PPD
Director, Clinical Development
Alexion Pharmaceuticals, Inc
Phone: PPD
Email: PPD

Protocol 19-515
Intraoperative
Hemostasis Assessment Form

Investigator is responsible for evaluating the endpoint of hemostatic efficacy. The Investigator will consult with the research team and surgical team, if applicable, and will be responsible for the interpretation of the endpoint prior to completing the hemostatic efficacy form.

Please complete this form and this will serve as a source document and be provided to the Endpoint Adjudication Committee.

- Estimate blood loss based on a particular surgery or surgery type
- Hemostasis evaluation period is from start of surgery to end of surgery, however hemostasis assessment is recorded at the end of the surgery
- **Predicated Blood Loss (mL):** Before an operation/incision, the Predicted Blood Loss should be estimated for an ANTI coagulated patient based on previous experience, this is a subjective evaluation
- **Observed Blood Loss (mL):** Register the actual amount of blood **in ml** which was lost during the operation.
- **Hemostasis Assessment** – This is subjective Hemostasis Assessment to be compared against normal non-anti-coagulated situations based on the 4-items scale (from excellent to poor)

Hemostasis Assessment			
Subject Number		Staff Completing Form	
Date entry into operation room		Time entry into operating room (24 Hr Clock)	
Type of surgical intervention		Predicted Blood Loss (mL) Determined prior to first incision	
Start date of surgery		Start time of surgery (24 Hr)	
End date of surgery		End time of surgery (24 Hr)	
Date of exit from operating room		Time of exit from operating room (24 Hr)	

Hemostatic Efficacy: Investigator Assessment – Treatment Day 1			
Was there any unexpected blood loss due to surgical complications	☐ Yes, comment: ☐ No	Observed Blood Loss (mL) Determined at end of surgery	
Date of Hemostasis Assessment		Time of Hemostasis Assessment	

Category	Definition	Investigator Assessment (check only 1 category)
Excellent	Normal hemostasis during the procedure	
Good	Mildly abnormal hemostasis as judged by quantity of blood loss (e.g. slight oozing from surgical wounds)	
Moderate	Moderate abnormality in intraprocedural hemostasis (e.g. controllable bleeding) but no need for additional systemic procoagulant product	
Poor	Severe hemostatic abnormality during the procedure (e.g. severe refractory hemorrhage) and need for additional systemic procoagulant products	

Investigator Name:	Signature:	Date:

1 April 2021

Protocol: 19-515 Protocol Amendment #2: 20 July 2020

Administrative Change Letter #1

Reason for Letter: Provide clarification that the adverse event (AE) selection in the CRF is different from the protocol and antibodies against host cell proteins (HCPs) are not being measured and analyzed.

To those sites participating in the above named and numbered clinical study, this letter serves to inform you about the following administrative changes to the above referenced protocol version.

Clarification: Section 9.2.2. Assessment of Causal Relationship

- Removal of causality assessment categories; probably, possible, unlikely, unrelated
- Causality to be assessed on a binary scale of related and unrelated

Rationale: Standardizing collection of severity and causality according to Alexion Global Drug Safety Standards.

Clarification: Section 9.2.3. Assessment of Severity

- Removal of Grades
- Removal of 'life-threatening consequence or urgent intervention indicated'.
- Removal of 'event results in Death'.

Rationale: Standardizing collection of severity and causality of AEs according to CDISC/CDASH guidelines. "Life-threatening" events are collected using a separate variable on the adverse event form. Death is collected as an outcome.

Clarification: Section 10.2.5., 11.7.7., Schedule of Assessments
Antibodies against HCPs are not being determined for the study.

Rationale: A Generation 2 HCP assay has not been developed. Results from previous studies indicate that the immunogenicity is low, therefore there is no value in continuing the assay.

Please file this letter and any IRB/EC correspondence with all copies of the protocol in the Investigator Site File and in all pertinent repositories in which the protocol is maintained.

If there are any questions concerning these changes, please contact us. These changes will also be captured in any future protocol amendment.

PPD

PPD

Global Medical Director Hematology
Alexion Pharmaceuticals, Inc
Phone: PPD Email: PPD

Alexion Confidential

Protocol 19-515:

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO REQUIRE URGENT SURGERY (ANNEXA-S)

Protocol Amendment 2.1 (Japan)

MEDICAL MONITOR： PPD, MD
Director, Clinical Development
Alexion Pharmaceuticals, Inc.
Phone: PPD
Fax: PPD
email: PPD

PROTOCOL DATE： Original: 16 September 2019
Amendment 1: 19 November 2019
Amendment 2: 20 July 2020
Amendment 2.1 (Japan): 15 March 2021

SPONSOR SIGNATORY：

PPD

15-Mar-2021 | 19:50:55 EDT

_____ _____
Director, Clinical Development **DATE**

Confidentiality Statement

This protocol is the property of the Sponsor. It is a confidential communication. Acceptance implies an agreement not to disclose information contained herein that is not otherwise publicly available, with the exception that it may be disclosed to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the purpose of obtaining approval to conduct the study. The IRB/IEC is requested and expected to maintain confidentiality. This document may not be used or published without the consent of the Sponsor.

INVESTIGATOR'S AGREEMENT

I have read the attached protocol amendment and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Signature of Principal Investigator

Name of Principal Investigator (Print) Date (DD Month YYYY)

Amendment Rationale:

The amendment is prepared for executing the study under the regulatory requirements and medical practice in Japan. This country-specific amendment changed a part of the protocol contents and applies to all subjects enrolled in Japan.

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63	9.2.2. Assessment of Causal Relationship	Added the following underlined statement. Before: An AE with causal relationship not initially determined will require follow-up to assign causality. Importantly, lack of efficacy does not necessarily constitute relatedness to study drug. After: An AE with causal relationship not initially determined will require follow-up to assign causality. Importantly, lack of efficacy does not necessarily constitute relatedness to study drug. <u>For any analyses of AE data, the assessments of 'unrelated' and 'unlikely' will be combined into the category of 'unrelated', and the assessments of 'possible' and 'probable' will be combined into the category of 'related'.</u>

Certificate Of Completion

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Signatures: 1
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Signer Events	Signature	Timestamp
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Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	15-Mar-2021 | 19:36
Certified Delivered	Security Checked	15-Mar-2021 | 19:49
Signing Complete	Security Checked	15-Mar-2021 | 19:50
Completed	Security Checked	15-Mar-2021 | 19:50

Payment Events	Status	Timestamps

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO REQUIRE URGENT SURGERY (ANNEXA-S)

DRUG NAME:	Andexanet alfa (PRT064445)
PROTOCOL NUMBER:	19-515
PHASE:	2
EUDRACT NUMBER	2020-000374-21
IND NUMBER	15089
NCT NUMBER	NCT04233073
TRIAL SPONSOR:	Portola Pharmaceuticals, Inc. PPD South San Francisco, CA 94080
MEDICAL MONITOR:	PPD, MD Executive Director Clinical Development Portola Pharmaceuticals, Inc. Phone: PPD Fax: PPD email: PPD
PROTOCOL DATE:	Original: 16 September 2019 Amendment 1: 19 November 2019 Amendment 2: 20 July 2020

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

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_____
Signature of Principal Investigator

_____ _____
Name of Principal Investigator (Print) Date (DD Month YYYY)

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PPD

PPD , MD

Date (DD Month YYYY)

Executive Director
Clinical Development
Portola Pharmaceuticals, Inc.

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OVERVIEW OF CHANGES IN THE CURRENT PROTOCOL AMENDMENT

Protocol Version: Date	Summary of Key Changes	Rationale for Change
Amendment 1: 19 Nov 2019	1. Revised study phase from 3b/4 to 3.	Phase clarified.
	2. Description of site locations revised.	Language changed to be less restrictive.
	3. Revised efficacy and safety objectives.	Objectives revised to add clarity, including which safety parameters will be measured.
	4. Added additional exploratory endpoints. Revised time of analysis of several endpoints from start to end of surgery. (Clarifications, were made throughout the synopsis, body of the document, and Appendices consistent with this change.)	Revised to align with objectives and to measure specific parameters.
	5. Revised Study Design with respect to timing, included new assessments, and identified the patients included in the Efficacy Analysis Population	Revised for clarity.
	6. Study Periods section was modified and timing of dosing revised	Language modified to remove ambiguity and clarify timing of dosing in relation to surgery.
	7. Revised language in eligibility criteria (and made additional edits throughout the body of the protocol for consistency).	Clarified multiple inclusion criteria, added assessment for anti-fXa activity level, and added additional exclusion criteria.
	8. Modified language in Synopsis and Section 6.2 regarding bolus timing, dosing, and surgery details as well as re-dosing or extended infusion criteria.	Language clarified.
	9. Revised sample size estimates, and revised Statistical Analysis Methods for Efficacy to remove null and alternative hypothesis testing.	Revised language to account for possible attrition rates and rare events and to more accurately reflect planned analyses.
	10. Statistical Analysis Methods for Safety was revised and use of the Safety Analysis Population noted.	The text was revised to include additional safety assessments and clarify the use of the Safety Analysis Population for safety analyses.
	11. Section 1.4 was updated to current clinical trial experience.	Modified to align with IB.
	12. Section 3.4.1 Study Population language revised and added to protocol regarding potential risks.	Language added to more accurately detail potential risks.
	13. Added rationale sections associated with dosing.	Added to explain rationale.
	14. Added precautions to Section 3.5 and revised Section 3.6 to include additional details regarding urgent surgeries.	Added to mitigate risks to patients.

Protocol Version: Date	Summary of Key Changes	Rationale for Change
Amendment 1: 19 Nov 2019 (Cont'd)	15. Informed consent text was removed from Section 4.3	Removed text to clarify the informed consent process.
	16. Text was added to follow-up safety procedures in Section 4.4.	Clarified the follow-up safety procedures.
	17. Section 5 was clarified and language added in regards to assessments, how patients are identified, Screening assessments, visit procedures and rationale for dose selection, unscheduled visits, and Early Termination visits.	Language changed to be inclusive of all assessments/ procedures and to provide clarity, to clarify how patients are identified and the assessments performed during Screening, additional information to be captured at unscheduled visits specified, and removed chemistry laboratory assessments from required assessments at Early Termination visit.
	18. In Section 7, text was removed regarding criteria for poor hemostatic efficacy. Text was added to describe when and how a second dose of adexanet shall be delivered.	Removed/added to clarify the text.
	19. In Section 10, language was added and subsections added regarding baseline assessments, informed consent, demographics, medical history, prior and concomitant medications, anticoagulant use, ASA PS classification, eligibility, patient identification number assignment, assessments performed at the central laboratory, physical examination, weight, clinical laboratory testing, intraoperative and hospitalization assessments, surgical intervention, interoperative blood loss, intraoperative hemostasis, blood products and hemostatic treatments, bleeding-related diagnostic and therapeutic procedures, recording duration in hospital care units, and end of study assessments. Numbering was revised as appropriate.	Language was added to provide information and clarify these topics in the protocol, including when/how informed consent is obtained, what demographics characteristics, medical history, and prior and concomitant medications will be captured at Baseline. The change clarifies the ASA PS assessment performed at Baseline, how eligibility will be assessed, and how/when patient identification numbers are assigned. The change to the protocol allows for broad physical examination, describes the assessments performed during and following surgery, provides details on requirements for surgical intervention, describes procedures for reporting blood loss during surgery, and use of blood products, other homeostatic procedures, diagnostic procedures, and therapeutic procedures before during and after surgical procedures. Procedures of reporting the duration of time spent in the hospital and end of study assessments were added.

Protocol Version: Date	Summary of Key Changes	Rationale for Change
Amendment 1: 19 Nov 2019 (Cont'd)	20. In Section 11, text was added regarding the Efficacy Analysis Population inclusion criteria. The primary efficacy endpoint language was revised and postoperative major bleeding events specified as adjudicated by the EAC in the Adverse Events section (11.7.1). The reason for collecting but not formally analyzing certain fXa activity levels added, and the role of the planned interim analysis added.	Language added for clarity
	21. Additional clarifications, deletions, and administrative corrections were made throughout the Synopsis, Investigator's Agreement, body of the document, References, and Appendices.	Edited to improve clarity and consistency and remove redundancy.
Amendment 2: 20 Jul 2020	1. Revised study phase from Phase 3 to Phase 2.	Revised to more accurately reflect study objectives of efficacy and safety.
	2. Language added to the Synopsis, Introduction, and Study Design to acknowledge evaluation of dosing.	Added to clarify that information obtained will include the adequacy and duration of andexanet dosing.
	3. Clarified when the DSMB would review safety data.	Provides additional detail on frequency of safety monitoring.
	4. Added Section 3.4.2 Rationale for the Study, with subsections 3.4.2.1 and 3.4.2.2.	Added to clarify the unmet medical need and to address current treatment options.
	5. Clarified that study termination may be recommended by the DSMB.	Clarified to provide guidance on study termination criteria.
	6. Added more language about safety monitoring and thrombosis risk.	Added to clarify that close monitoring will occur when thrombosis risk is highest.
	7. Added language to Section 3.6 about the detrimental effects of postponing surgery.	Added to clarify the unmet medical need and to address current treatment options
	8. Added Section 3.7 Acknowledgement of Benefit:Risk During COVID-19 Pandemic.	Added to address concerns associated with the pandemic and relevant study procedures and to acknowledge recent guidance on this topic.

Protocol Version: Date	Summary of Key Changes	Rationale for Change
Amendment 2: 20 Jul 2020 (Cont'd)	9. Revised language in eligibility criteria (and made additional edits throughout the body of the protocol for consistency): a. Revised inclusion criterion 4 to more clearly outline FXa inhibitor timing and dosing. b. Revised inclusion criterion 6 from "medically acceptable" methods of contraception to "highly effective" methods of contraception. c. Revised exclusion criterion 3 to remove specific cardiovascular procedures. d. Revised exclusion criterion 9 to remove "severe" so that the criterion only refers to "sepsis," as opposed to "severe sepsis." e. Added "at time of Screening" to exclusion criterion 11. f. Added exclusion criteria 18, 19, and 20.	Revised to more accurately reflect specific details and intent of the eligibility criteria.
	10. Included language in Section 5.2 that mortality would be conducted by phone for the Day 30 visit and that the entire Day 30 visit may be conducted by phone. Additional changes were made throughout the document for alignment purposes, as needed.	Included to minimize nonessential hospital/clinic visits during the pandemic.
	11. Added allowance of 2.5 mg of apixaban to Table 2 under the category of low dose if < 8 hours.	Added to align with threshold stated in exclusion criterion 13.
	12. Added Section 7.2.4.	Added to address prohibited and permissible procedures associated with other trials.
	13. Clarified re-dosing details in Section 7.3 and other subsections, as needed.	Revised for clarity.
	14. Added Section 8.3 Intraoperative Rescue Strategies.	Added a section to address possible intraoperative rescue strategies.
	15. Added language to Section 9.2.4.9 regarding contraception use, and aligned other text within the body of the document.	Added to clarify that highly effective contraception should be used.
	16. Added language to Section 10.2 Central Laboratory Testing.	Added to include details about the collection, processing, storage, and destruction of samples.
	17. Clarified which study population would be used to analyze efficacy endpoints and language that specifies that no interim efficacy analyses will be conducted.	Provided more precise language about study populations and efficacy analyses.

Protocol Version: Date	Summary of Key Changes	Rationale for Change
Amendment 2: 20 Jul 2020 (Cont'd)	18. Added 2 exploratory endpoints associated with intraoperative blood loss. Study objectives were updated to acknowledge these additional endpoints, and additional language was included in Section 10.4.2 and the SOA regarding predicted blood loss.	Added because these are endpoints of interest. Changes to Section 10.4.2 and the SOA were made for clarity and consistency.
	19. Reduced planned sample size from 200 patients to 100 patients and modified language in Section 11.6 Determination of Sample Size.	Reduced sample size to align with goals for a Phase 2 study.
	20. Modified language in Section 13.2 Informed Consent to include acknowledgement that proxy consents must be permissible by national regulatory authorities and that emergency consent is not permitted.	Modified to clarify informed consent conduct to conform with applicable regulations.
	21. Added language to acknowledge that the study will be conducted in compliance with the General Data Protection Regulation.	Modified to conform with applicable regulations.
	22. Edited SOA: a. Revised column for Day 3 (from 72 hours to 48 hours). b. Added a row for "Estimate Predicted Blood Loss." c. Modified table header. d. Added "EoS + 6 h" column and specified sample collection at that time point. e. Revised footnotes for alignment.	Edited to correct a typo, for clarity on timing of andexanet dosing and surgery, and to include additional samples per clinical guidance.
	23. Revised Appendix C and added Table 4.	Revised to remain current with the definition of sepsis, and removed "severe" from the descriptions.
	24. Additional references were added as needed.	Added to support content.
	25. Additional clarifications, deletions and administrative corrections were made throughout the Synopsis, Title Page, body of the document, References, and Appendices.	Edited to improve clarity and consistency.

LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
andexanet alfa	Recombinant factor Xa inhibitor antidote, PRT064445
ASA	American Society of Anesthesiologists
AUC	Area under the curve
CABG	Coronary artery bypass grafting
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed concentration
COVID-19	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
CT	Computed tomography
cTn	Cardiac troponin
D-dimer	Fibrin degradation product
DIC	Disseminated intravascular coagulation
DOAC	Direct oral anticoagulant
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ERCP	Endoscopic retrograde cholangio-pancreatography
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
EMA	European Medicines Agency
ETP	Endogenous thrombin potential
EU	European Union
F1+2	Prothrombin fragment 1 and 2
FDA	(United States) Food and Drug Administration
FFP	Fresh frozen plasma
FIO_2	Fraction of inspired oxygen

Term	Definition
FX	Factor X
FXa	Factor Xa (activated factor X)
GCP	Good Clinical Practice
HCP	Host-cell protein
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
LBBB	Left bundle branch block
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
min	Minute
MRI	Magnetic resonance imaging
nAb	Neutralizing antibody (activity)
NOAC	Novel oral anticoagulant
OR	Operating room
PACU	Post-anesthesia care unit
PaO_2	Partial pressure oxygen-arterial
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PRBC	Packed red blood cell
PS	Physical status
PT	Prothrombin time
RBC	Red blood cell

Term	Definition
rfVIIa	Recombinant factor VIIa
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
ST-T	ST-segment T wave
t½	Terminal half-life
TAT	Thrombin-antithrombin
TE	Thrombotic event
TEAE	Treatment-Emergent Adverse Event
Temp	Temperature
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TG	Thrombin generation
TIA	Transient ischemic attack
TXA	Tranexamic acid
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist
VQ	Ventilation-perfusion
VTE	Venous thromboembolism
WBC	White blood cells
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study Title	Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)
Study Number	19-515
Study Phase	2
Number of Sites	Approximately 80 sites globally
Objectives	In patients requiring urgent surgery who are being treated with a direct or indirect Factor Xa (FXa) inhibitor, the objectives of this study are as follows: **Primary Objective:** • To evaluate hemostatic efficacy following andexanet alfa (andexanet) treatment. **Secondary Efficacy Objective:** • To evaluate the effect of andexanet on anti-fXa activity. **Exploratory Efficacy Objectives:** • To evaluate the effect of andexanet on thrombin generation (TG). • To evaluate the use of red blood cell (RBC) transfusions. • To evaluate the use of non-RBC, non-platelet blood products and hemostatic agents. • To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir. • To evaluate the time from obtaining informed consent (study consent) to the start of surgery. • To evaluate observed intraoperative blood loss and the difference between predicted versus observed blood loss. • To evaluate the length of index hospitalization, intensive care unit (ICU) stay, time in a post-anesthesia care unit (PACU), time in the operating room (OR), and length of surgery. • To evaluate the occurrence of re-hospitalization. • To evaluate the occurrence of post-surgical major bleeding. • To evaluate the occurrence of re-operations for bleeding. • To evaluate the effect of andexanet on tissue factor pathway inhibitor (TFPI) activity. • In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity. **Safety Objective:** • To evaluate the overall safety of andexanet.
Efficacy Endpoints	**Primary Efficacy Endpoint:** • The achievement of hemostatic efficacy as determined by the surgeon's assessment of intraoperative hemostasis and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC).

	Secondary Efficacy Endpoint: • The percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion. **Exploratory Endpoints:** • Relationship between hemostatic efficacy and anti-fXa activity. • Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, number of patients with percent reduction from baseline > 80%. • Reversal of anticoagulant effect as measured by TG parameters (with endogenous thrombin potential as the primary measure). • Occurrence of receiving 1 or more RBC transfusions from the start of the andexanet bolus through 12 hours after the end of surgery. • The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the end of surgery. • The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery. • Observed amount of intraoperative blood loss. • Difference between observed blood loss and predicted blood loss. • Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery. • Length of time from the signing of informed consent to the start of surgery. • Length of time from clinical presentation at the treating facility to the start of surgery. • Length of index hospitalization, assessed at the Day 30 visit. • Time hospitalized in a PACU, assessed at the Day 30 visit. • Time hospitalized in an ICU, assessed at the Day 30 visit. • Length of surgery. • Time in the OR. • Occurrence of re-hospitalization, within 30 days of enrollment, including number of days and length of re-hospitalization (through 30 days post enrollment). • Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and Haemostasis (ISTH) criteria, within 12 hours after the start of the initial surgery. • Occurrence of re-operations for bleeding, including surgical wound hematomas, within 12 hours after the end of the initial surgery. • Change from baseline in TFPI activity post-administration of andexanet. • Change from baseline in anti-IIa activity (only patients taking enoxaparin).
Safety Measurements	• Adverse events (AEs) (including serious AEs [SAEs]), vital signs, physical examinations, and clinical laboratory measurements. • Thrombotic events (TEs) within 30 days of enrollment, including suspected and confirmed by adjudication. • Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality. • Antibodies to FX, FXa, andexanet, and host-cell proteins (HCPs).

Study Design	This is a Phase 2 multicenter, prospective, open-label, proof-of-concept study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery, and who have, within 15 hours prior to surgery, received their last dose of 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. In addition to the objectives mentioned above, information obtained from this study is expected to include dosing considerations (adequacy of dosing and duration of dosing required) that will be used to inform a subsequent randomized Phase 3 trial for registrational purposes. Prior to any study procedures, each patient must be provided with oral and written information describing the nature and duration of the study, and the patient must sign a written informed consent form in a language in which he/she is fluent before study-specific procedures are conducted. Due to the critical nature of the illness under study and the possibility that patients will be unable to provide their own consent, proxy consents (defined as consent from a legally authorized representative) are allowed if permissible by national regulatory authorities or local/regional laws and regulations. Emergency consent is not permitted. If the time from last dose of an FXa inhibitor is unknown, or greater than 15 hours prior to surgery, the patient may be enrolled provided a local laboratory anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin). Patients enrolled in this manner should receive a high-andexanet dosing regimen. In such cases the start of surgery must begin no greater than 4 hours after the blood collection for the local anti-fXa activity test. The prespecified time periods and anti-fXa activity level thresholds are designed to ensure patients have sufficiently high anti-fXa activity levels. The Efficacy Analysis Population for the study will only include patients whose central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin). The start of surgery must be within 15 hours following the last dose of FXa inhibitor. Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an intravenous (IV) bolus administered over 15 to 30 minutes (depending on dose) immediately prior to the start of surgery (skin incision). The bolus must be completely administered before the start of surgery (i.e., at the first incision; designated Time 0). The bolus must be immediately followed by an IV infusion that will continue for a minimum of 2 hours, irrespective of the duration of the surgery. The infusion should continue from start to end of surgery (skin incision to skin closure). The treating surgeon will assess hemostatic efficacy at the conclusion of the procedure (i.e., skin closure, or, if skin closure is not completed by intention, an equivalent milestone such as dressing or packing the surgical incision). Additional andexanet, be it for extended infusion or re-dosing, may be given at the discretion of the Investigator when specific criteria are met (see "Test Product, Dose, and Mode of Administration" below). Procedural risks inherent to the urgent surgical procedure itself would vary based on the procedure type and individual patient risk factors, and should be additionally communicated to the patient by the treating physician. The safety monitoring plan for this study is robust. It is expected that patients requiring urgent surgery will remain hospitalized for at least 12 hours. During the first 12-hour period (Study Day 1), AEs, vital signs, physical examinations, and laboratory testing will be performed to monitor safety. It is recommended that the Investigator carefully weigh the risk of new bleeding against the risk of thrombosis when considering when to resume anticoagulation for the patient. Survival status will be ascertained on Study Day 30, and, if applicable, cause of death will be recorded. Antibody

	samples will be taken at baseline and Day 30 to assess immunogenicity against andexanet, FX, FXa, neutralizing antibodies, and HCPs. The Day 30 visit may be conducted by phone if necessary to minimize nonessential visits. The independent EAC will adjudicate all deaths, TEs, post-surgical bleeding events (e.g., surgical hematomas), and hemostatic efficacy. The independent EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data approximately every 6 months and will be empowered to recommend modifying or stopping the trial for safety reasons if warranted. All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. In addition, patients who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit.
Study Periods	The study duration for any individual patient will be up to 37 days. There are 4 study periods. Study periods are defined as follows: • Screening Period: Day 1. • Pre-surgical Assessment Period: Day 1. • Treatment Period: Day 1. o Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~2.5 hours) but no greater than a total 6.5 hours (including both the initial regimen and the extended infusion). o Re-dosing (low dose bolus and infusion) may occur within 12 hours after completion of the first course of andexanet treatment (but after the conclusion of the surgical procedure) if protocol specified criteria are met, at the investigator's discretion. • Safety Follow-up Period: Days 1–30 + 7.
Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or their medical proxy (or legal designee) has given written informed consent. 2. Age ≥ 18 and < 85 years old. 3. Requires urgent surgical intervention that must occur within 12 hours of consent, for which reversal of anti-fXa activity is judged necessary. 4. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], edoxaban [last dose 30 mg or greater] or enoxaparin [≥ 1 mg/kg/d]): 5. ≤ 15 hours prior to start of surgery. 6. > 15 hours prior to start of surgery or unknown time from the last dose, if documented anti fXa activity is > 100 ng/mL (> 0.5 IU/mL for enoxaparin, or over the equivalent IU/mL threshold on a low molecular weight heparin assay; see Laboratory Manual) within 2 hours prior to consent. Note: Patients enrolled in this manner should receive a high-andexanet dosing regimen. 7. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential). 8. Willingness to use highly effective methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).

Exclusion Criteria	If a patient meets any of the following criteria, he or she is not eligible: 1. Surgery for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low. 2. Acute life-threatening bleeding (ISTH criteria) at the time of Screening: a. The patient has acute-overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained. b. The patient has overt bleeding associated with a fall in hemoglobin level by ≥2g/dL, OR, a hemoglobin ≤8 g/dL if no baseline hemoglobin is available. c. The patient has acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal. 3. Any surgical procedure that involves the intraoperative use of systemic, intravascular, unfractionated heparin. 4. Primary procedure for efficacy assessment is a non-surgical interventional procedure (e.g, lumbar puncture, skin biopsy, cardiac catheterization, endoscopic retrograde cholangio-pancreatography). 5. Expected survival of < 1 month due to comorbidity. 6. Known "Do Not Resuscitate" order or similar advanced directive. 7. The patient has a recent history (within 30 days prior to screening) of a diagnosed TE as follows: venous thromboembolism (including deep vein thrombosis, pulmonary embolism, intracardiac thrombus), myocardial infarction (including asymptomatic troponin elevations), disseminated intravascular coagulation, acute traumatic coagulopathy, cerebrovascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease. 8. Acute decompensated heart failure or cardiogenic shock at the time of screening. 9. The patient has sepsis or septic or severe hemorrhagic shock at the time of Screening. 10. The patient has heparin-induced thrombocytopenia (with or without thrombosis). 11. Inherited coagulopathy (e.g., anti-phospholipid antibody syndrome, protein C/S deficiency, Factor V Leiden) at time of Screening. 12. Platelet count < 80,000/μL at the time of Screening. 13. Last dose of apixaban < 2.5 mg, rivaroxaban < 10 mg, edoxaban < 30 mg, or enoxaparin 40 mg. 14. The patient is pregnant or a lactating female. 15. The patient has received any of the following drugs or blood products within 7 days of enrollment: o Vitamin K antagonists (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (e.g., NovoSeven®). o Whole blood, plasma fractions. Note: Administration of tranexamic acid, platelets or packed red blood cells is not an exclusion criterion. 16. The patient was treated with an investigational drug < 30 days prior to Screening. 17. Prior treatment with andexanet. 18. Known hypersensitivity to any component of andexanet. 19. Known allergic reaction to hamster proteins. 20. Known or suspected (i.e., presumed positive) COVID-19-related illness at the time of Screening.

Test Product, Dose, and Mode of Administration

The andexanet IV bolus will be initiated within 30 minutes prior to the start of surgery (i.e., the first incision) and must be completed prior to surgery start. The bolus will be followed by a continuous infusion lasting at least 120 minutes, irrespective of the length of the surgery. The continuous infusion must be ongoing at the start of surgery, and must continue until the end of surgery even if extended treatment is required. There are 2 possible dosing regimens as described below:

Andexanet Dose	Timing of Last Dose of FXa Inhibitor	Initial Dose		Extended Infusion
		Initial IV Bolus	Initial Follow-on IV Infusion	
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban 10 mg • Apixaban 2.5-5 mg • Enoxaparin 40 mg • Edoxaban 30 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery	Extended infusion (beyond 120 minutes) may be administered at **4 mg/min** (low-dose) for up to 4 additional hours *
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **> 15 hours or unknown time** • Local anti-fXa > 100 ng/mL (0.5 IU/mL for enoxaparin)	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery	

*** Extended Infusion (Additional low-dose 4mg/min infusion up to 4 hours)**

Following the primary andexanet bolus and 120-minute infusion, the andexanet infusion will be continued at the low dose of andexanet (4 mg/min) if the surgery extends longer than the primary bolus and infusion. The extended infusion (1) must continue at least through the end of the surgery and (2) may additionally continue during the immediate post-operative period (per investigator discretion), and (3) should not exceed 4 hours.

Maximum Length of Dosing (Initial Bolus + 120 minute Infusion + Extended Infusion, < 6.5 hours):

The total duration of dosing including initial bolus, 120-minute infusion, and any extended infusion, should not exceed 6.5 hours. The limit of planned duration of infusion is stipulated to balance declining anti-fXa plasma levels and acceptable exposure to andexanet.

	Criteria for Re-Dosing with Andexanet Consider re-dosing with andexanet (**low-dose bolus + 120 min infusion**) only if: a) New, clinically significant, surgery-related post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b) The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c) Re-dosing initiation occurs within 12 hours after the completion of the surgical procedure.
Reference Therapy, Dose, and Mode of Administration	Not applicable.
Sample Size	Approximately 100 patients will be enrolled. After accounting for 20% attrition (e.g., canceled surgeries, discontinued and/or non-evaluable patients, or baseline anti-fXa activity analyzed by central laboratory less than the evaluability threshold), a sample size of 80 patients will provide an estimate of the proportion of patients achieving effective (excellent or good) hemostatic efficacy with a margin of error (half width of the 95% confidence interval [CI]) that is less than 11%.
Statistical Analysis Methods for Efficacy	All efficacy analyses will be performed in the Efficacy Analysis Population. Unless otherwise specified, all CIs will be 2-sided and reported at the 95% confidence level. The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI. The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.
Statistical Analysis Methods for Safety	All safety analyses will be performed in the Safety Analysis Population. Safety will be assessed by examination of 30-day survival status, AEs (including SAEs and TEs), vital signs, physical examination, centrally adjudicated deaths, clinical laboratory measurements, and antibodies to andexanet, FX, FXa, and HCPs. These data will be descriptively summarized. All potential post-surgical major bleeding events and TEs will be confirmed by adjudication.

1.0 INTRODUCTION

1.1. Background

The class of oral anticoagulants known as direct Factor Xa (FXa) inhibitors (Direct Oral Anticoagulants [DOACs]) has consistently demonstrated comparable or superior efficacy and/or safety relative to its predecessors, Vitamin K Antagonists (VKAs) and Low Molecular Weight Heparins. These agents (apixaban [Eliquis®], betrixaban [BevyxXa®], edoxaban [Savaysa®], rivaroxaban [Xarelto®]) are approved for the prevention of serious thromboembolic outcomes (e.g., stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], venous thromboembolism [VTE] in hip or knee replacement surgery) and have become widely used in the United States (US) and globally. One limitation to the use of FXa inhibitors has been the lack of an antidote to be used in cases of severe and/or life-threatening bleeding events or urgent or emergency surgery. In the case of the latter, it has been estimated, based on analyses from pivotal studies of direct FXa inhibitors, that approximately 1% of anticoagulated patients may require urgent surgery within 2 years of initiation [1, 2]. As the use of DOAC agents increase, the need to reverse anticoagulation related to this class of drugs is expected to increase.

Andexanet, a rationally designed, recombinant analog of endogenous human FXa, has been developed to rapidly and potently reverse FXa inhibition and restore physiologic coagulation. Data from Phase 2, Phase 3, and ongoing Phase 3b/4 studies have shown that andexanet rapidly reverses FXa inhibition in healthy volunteers and in bleeding patients [3]. Andexanet is also associated with a high rate of clinical hemostasis in patients with acute major bleeding [4]. Importantly, however, andexanet has not been evaluated in patients requiring urgent surgery. The present Phase 2, proof-of-concept trial will be performed to evaluate hemostatic efficacy and safety of andexanet in patients requiring urgent surgery receiving an oral FXa inhibitor. Additionally, information obtained from this study will include the adequacy and duration of andexanet dosing. The results of this study will be used to inform a subsequent randomized Phase 3 trial for registrational purposes.

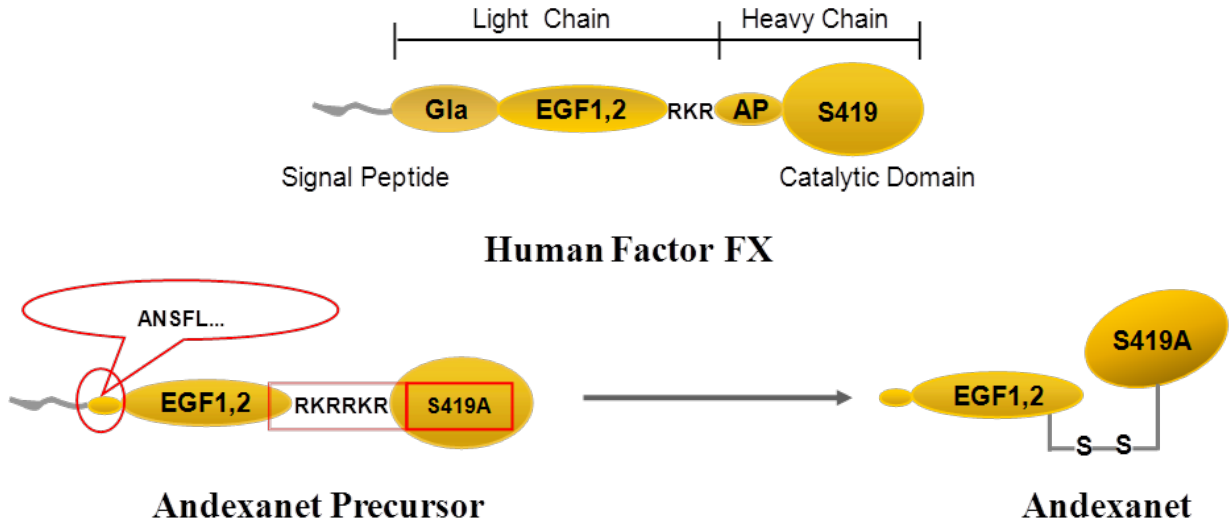
Andexanet was granted accelerated approval by the US Food and Drug Administration (FDA) on 03 May 2018 and was granted conditional marketing authorization by the European Commission on 26 April 2019, for the treatment of patients with life-threatening bleeding while taking apixaban and rivaroxaban. The confirmatory randomized controlled trial in patients with intracranial hemorrhage, ANNEXA-I, is currently ongoing. Andexanet is not currently indicated for FXa reversal in patients requiring urgent surgery.

1.2. Description of Andexanet

Andexanet is a recombinant version of human FXa that has been modified to render it functionally inactive (Figure 1). To achieve this aim, 2 key structural modifications were made to native human FXa. First, the substitution of a serine residue with an alanine at the active site eliminated the protein's catalytic activity. Second, the removal of the Gla domain eliminated the ability to assemble into a prothrombinase complex, thereby removing potential intrinsic anticoagulant effects. Reversal of anticoagulation is achieved because andexanet retains the ability to bind FXa inhibitors with high affinity, thereby sequestering them and preventing them from binding to and inhibiting native FXa.

Additional information about the mechanism and structure of andexanet can be found in the Investigator's Brochure.

Figure 1: Structures of Human Factor X and Andexanet



1.3. Summary of Relevant Nonclinical Experience with Andexanet

Nonclinical studies in several species (mice, rats, rabbits, pigs, and cynomolgus monkeys) have demonstrated that the anticoagulant effects of direct and indirect FXa inhibitors were reversed by andexanet, resulting in a return to normal hemostasis.

Functional studies with the direct FXa inhibitors have been undertaken to explore the effectiveness of andexanet to reverse injury-induced bleeding in anticoagulated animals using the well-characterized rodent tail transection models and a modified rabbit liver laceration model. In these studies, andexanet was administered either prior to (prophylactic model) or following (treatment model) organ injury to mimic the clinical settings of urgent (emergent) surgery or massive bleeding as a result of trauma. In both the prophylactic and treatment models, significant reductions in blood loss were observed in andexanet-treated animals vs vehicle controls. The decrease in blood loss following andexanet administration correlated with a decrease in pharmacodynamics (PD) markers of anticoagulation, including anti-fXa activity, international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time, depending on the inhibitor and species. Collectively, in these models, andexanet dose-dependently reduced the anticoagulant effects of the direct FXa inhibitors, requiring a minimum molar ratio of ~1:1, andexanet:direct FXa inhibitor for maximal inhibition of anti-fXa activity.

Andexanet has also been tested in a pig polytrauma model designed to evaluate its efficacy in a setting with a greater severity of bleeding. Using German landrace pigs anticoagulated with apixaban (20 mg/day for 4 days), the effect of an intravenous (IV) bolus (1,000 mg) of andexanet versus a bolus (1,000 mg) plus a 2-hour infusion (10 mg/min) was studied when andexanet was administered after crush injury to a single lobe of the liver, followed by bilateral femur fracture. Following andexanet treatment (12 minutes after injury) with a bolus alone, there was a rapid drop in anti-fXa levels to near zero, which returned to placebo levels ~2 hours later. With bolus plus infusion, the anti-fXa levels remained low throughout the duration of the infusion and then gradually returned to placebo levels approximately 2 hours after the end of infusion. With regard to bleeding, anticoagulation with apixaban resulted in an approximately 2-fold increase in blood loss 12 minutes after injury. In the control group (administered placebo), there was a subsequent increase in blood loss over time to 3,403 ± 766 mL, and 100% of the animals exsanguinated with a mean survival time of 135 minutes (range 92–193 minutes). Treatment with andexanet resulted in a significant reduction in total blood loss post-injury: 57% (1,264 ± 205 mL) and 59% (1,202 ± 94 mL) for bolus alone and bolus plus infusion of andexanet, respectively. All andexanet-treated animals survived for the duration of the observation period (5 hours).

The toxicology of andexanet was evaluated in both rats and monkeys. Because the intent was to administer andexanet to reverse the anticoagulant effect of FXa inhibitors and thereby restore baseline hemostasis, studies in monkeys were conducted with andexanet administered alone as well as co-administered with FXa inhibitors. Andexanet was well-tolerated in both species at all dose levels. The highest dose administered in both species was 60 mg/kg/day (single day [only in monkeys] and 2-week repeat dose studies) and was the No Observed Adverse Effect Level. In monkeys the 60 mg/kg/day dose resulted in exposure levels 2-3-fold above those observed in clinical studies at the high therapeutic dose.

1.4. Summary of Relevant Clinical Experience with Andexanet

Andexanet has been studied in approximately 545 healthy subjects thus far in Phase 1 to 3 studies, as well as in 352 patients presenting with an acute major bleeding event while receiving an FXa inhibitor in the ongoing Phase 3b/4 (ANNEXA-4) study. In addition, andexanet was administered to a single preoperative patient taking apixaban who required emergency surgery to treat necrotizing fasciitis [5]. Finally, there are 5 other ongoing studies; 4 in healthy volunteers: a Phase 2 study to investigate the reversal of the pharmacologic effects of the oral FXa inhibitor, betrixaban; a Phase 2 study to evaluate the pharmacokinetics (PK), PD, safety, and tolerability of andexanet in individuals of Japanese descent; and 2 Phase 1 studies to compare the PK of andexanet produced by 2 manufacturing processes; and 1 study in patients: a randomized controlled clinical trial to evaluate the clinical efficacy and safety of andexanet in patients with intracranial hemorrhage while taking direct FXa inhibitors.

Completed trials include a single ascending dose Phase 1 study (Study 11-501) in 32 healthy subjects; a Phase 1 study (Study 14-506) examining the PK and PD of andexanet in 10 young vs. 10 older subjects receiving apixaban; a Phase 1 PK/PD study (Study 16-512) to evaluate the PK, PD, safety, and tolerability of andexanet produced by an updated manufacturing process (Generation 2); a Phase 2 dose-ranging study (Study 12-502) in 157 healthy subjects to determine the appropriate doses to reverse the anticoagulant effects of apixaban, rivaroxaban, enoxaparin and edoxaban; and 2 Phase 3 studies in 148 healthy older subjects (50-75 years) to confirm that the doses defined in the Phase 2 study reverse apixaban (Study 14-503) or rivaroxaban (Study 14-504). Details of the completed studies may be found in the Investigator's Brochure.

1.4.1. Phase 1 Study of Andexanet Alone in Healthy Subjects (11-501)

Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and PD of andexanet in 32 healthy subjects, each of whom received 1 of 4 doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.6.

1.4.2. Phase 1 Study of Andexanet in Healthy Younger Versus Older Subjects (14-506)

Study 14-506 was a Phase 1 randomized, open-label study of andexanet in healthy younger (18-45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban for 3 hours and then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin generation (TG) in older and younger subjects were similar. The safety data from this study are summarized in Section 1.4.6.

1.4.3. Phase 1 PK/PD Study to Evaluate the PK, PD, Safety, and Tolerability of Andexanet Produced by an Updated Manufacturing Process (Generation 2) (16-512-Direct Inhibitors)

Study 16-512-Direct Inhibitors was a randomized, double-blind, placebo-controlled study in healthy volunteers dosed to steady state with FXa inhibitors, designed to: 1) demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes; 2) evaluate the degree to which Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo; and 3) evaluate the safety and tolerability of Generation 2 andexanet. A total of 122 subjects were enrolled in the study. Generation 1 and Generation 2 andexanet were found to have PK comparability when administered at low doses, though strict bioequivalence criteria were not met with high dose andexanet. That said, Generation 1 and Generation 2 andexanet were observed to be comparable for the primary PD parameter of anti-fXa activity at both low and high doses of andexanet. The safety data from this study are summarized in Section 1.4.6.

1.4.4. Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects (12-502)

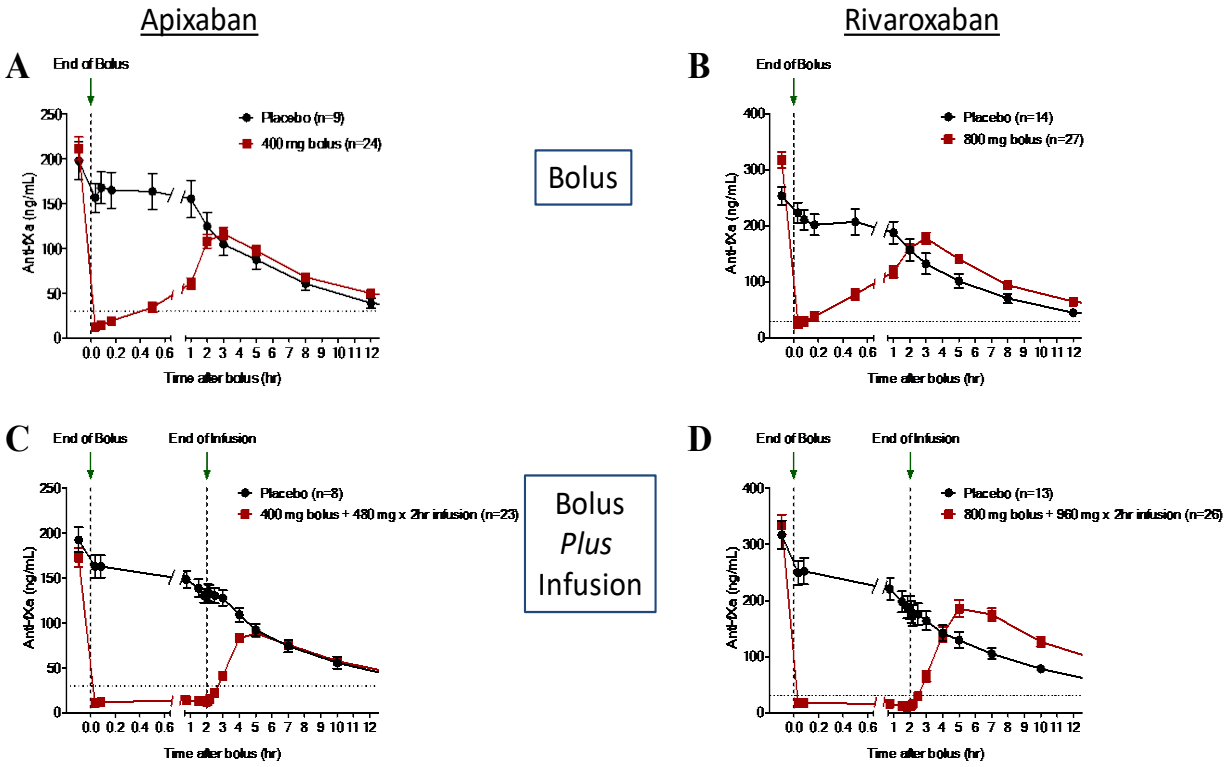
The dose-finding Study 12-502 was a Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in healthy subjects receiving 1 of 4 direct or indirect FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Each FXa inhibitor was examined in a separate study module, within which multiple dosing regimens of andexanet were given in cohorts of 9 healthy subjects (6 active, 3 placebo). The anticoagulant was dosed to steady state over 5 to 6 days, before administration of andexanet or placebo on Study Day 6. Depending on the anticoagulant dose, the total dose of andexanet across dosing cohorts ranged from 90 to 1,760 mg. Healthy subjects were then followed through Study Day 13 in a domiciled Phase 1 study unit and, subsequently, through Day 48 as outpatients.

Andexanet exhibited dose-proportional PK for both maximum observed concentration (C_{max}) and area under the curve (AUC) with a mean terminal half-life ($t_{½}$) of approximately 4 hours. Administration of andexanet also resulted in a dose-dependent reduction in anti-fXa activity for each of the FXa inhibitors. Additionally, the downstream anticoagulant effects of apixaban, rivaroxaban, and edoxaban were reversed in a dose-dependent fashion by administration of andexanet, as evaluated by the measurement of TG. These effects were consistent with restoration of hemostatic mechanisms after andexanet administration. The safety data from this study are summarized in Section 1.4.6.

1.4.5. Phase 3 Studies in Healthy Older Volunteers (14-503 and 14-504)

Two randomized, double-blind, placebo-controlled studies were designed to evaluate reversal of anticoagulation in older subjects (ages 50-75 years) anticoagulated with apixaban (Study 14-503) or rivaroxaban (Study 14-504). In these studies, the anticoagulant was dosed to steady state over 4 days (rivaroxaban) or 3.5 days (apixaban) before administration of andexanet or placebo on Study Day 4. The subjects were then followed through Study Day 8 in a domiciled Phase 1 study unit and, subsequently, through Day 43 as outpatients. Andexanet was administered either as an IV bolus (Part 1) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). Reversal of anticoagulation was measured using anti-fXa activity, anticoagulant free fraction, TG, and other coagulation markers. A single IV bolus of andexanet significantly reversed the anti-fXa activity of apixaban and rivaroxaban, reduced unbound apixaban and rivaroxaban concentrations, and restored normal TG (Figure 2), with the maximal effect observed within 2 minutes of the end of the bolus administration. The safety data from this study are summarized in Section 1.4.6.

Figure 2: Rapid Onset and Significant Reduction of Apixaban and Rivaroxaban Anti-fXa Activity in Older Healthy Subjects by Andexanet (Study 14-503 and Study 14-504)



fXa = activated factor X; hr = hour; IV = intravenous

Legend: Anti-fXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion.

A. Apixaban – with andexanet 400 mg IV bolus

B. Rivaroxaban – with andexanet 800 mg IV bolus

C. Apixaban – with andexanet 400 mg IV bolus plus 4 mg/minute infusion for 120 minutes

D. Rivaroxaban – with andexanet 800 mg IV bolus plus 8 mg/minute infusion for 120 minutes

Note: A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-fXa activity following andexanet treatment. The points on the graph represent the mean anti-fXa activity level and error bars illustrate standard error. There was a statistically significant difference ($P < 0.05$) in the percent change of anti-fXa activity normalized to pre-bolus between andexanet and placebo until 2 hours after administration of bolus (Part 1) or infusion (Part 2). The horizontal dashed-line represents the anti-fXa activity at 30 ng/mL, the estimated non-effective level for FXa inhibition [6].

1.4.6. Summary of Safety from Clinical Studies of Healthy Subjects

Andexanet has been generally well tolerated in healthy volunteers in the Phase 1, 2, and 3 studies at single doses up to 1,760 mg, with no apparent pattern of safety signals with the exception of mild-moderate infusion reactions. A single adverse event (AE) (bilateral pneumonia) met serious adverse event (SAE) criteria in the Phase 1 study 11-501. This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred approximately 3 weeks after

dosing. No severe or life-threatening AEs have been reported. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent, and have rarely required treatment (2 subjects received 1 dose each of diphenhydramine). With the exception of 2 subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting.

Andexanet was associated with dose-dependent increases in prothrombin fragment 1 and 2 (F1+2), thrombin-antithrombin (TAT), and fibrin degradation product (D-dimer), and with a concomitant decrease in tissue factor pathway inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with clinical evidence of thrombosis. Compared with administration of andexanet alone (Study 11-501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of an anticoagulant.

In all completed studies to date, among healthy subjects treated with andexanet, approximately 11% developed low-titer non-neutralizing antibody (nAb) to andexanet. There have been a small number of very low-titer non-nAbs to FX and FXa, with the titer value for all positive samples occurring at the minimum required dilution. However, there have been no nAbs to FX or FXa.

1.4.7. Phase 3b/4 Study in Patients with Acute Major Bleeding (14-505)

Study 14-505 (ANNEXA-4) is an ongoing, multi-national, prospective, open-label, single-arm clinical study of andexanet in patients with acute major bleeding while taking an FXa inhibitor (specifically apixaban, edoxaban, enoxaparin, or rivaroxaban). As of 01 June 2018, 352 patients had been enrolled in the study. Baseline characteristics included a mean age of 77 years, 47% female, 87% Caucasian, and median body mass index 27 kg/m^2. A total of 90 patients (26%) had gastrointestinal bleeding, 227 patients (64%) had an intracranial hemorrhage, and 35 patients (10%) had other types of bleeding.

Of the 352 enrolled patients, 254 were considered efficacy evaluable, defined as having a major bleed confirmed by adjudication, and a baseline anti-fXa activity of 75 ng/mL or greater ($\geq$ 0.25 IU/mL for enoxaparin patients). In efficacy-evaluable patients taking apixaban and rivaroxaban, the median reduction from baseline in anti-fXa activity was > 90%. Overall, of 249 patients with evaluable hemostatic efficacy, 204 (81.9%) had excellent or good hemostatic efficacy. Of these, 171 (68.7%) were adjudicated as having excellent hemostatic efficacy and 33 (13.3%) as having good hemostatic efficacy. Of the efficacy evaluable patients presenting with intracranial hemorrhage, the rate of excellent or good hemostatic efficacy was 80.4%.

Of the 352 patients in the Safety Population, 250 patients (71.0%) experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs (occurring in ≥ 5% of patients) by preferred term were urinary tract infection in 31 patients (8.8%) and pneumonia in 21 patients (6.0%). A total of 32 patients (9.1%) experienced AEs that were considered by the Investigator to be possibly or probably related to andexanet. The most frequent treatment-related events were pyrexia (4 patients; 1.1%), ischemic stroke (4 patients; 1.1%), and headache and nausea (3 patients each; 0.9%).

Serious adverse events were experienced by 144 patients (40.9%). The most common SAEs (occurring in ≥ 2% of patients) were pneumonia in 11 patients (3.1%) and respiratory failure in 9 patients (2.6%). Seventeen (4.8%) patients experienced at least 1 treatment-related SAE. The most frequently reported SAEs that were considered by the Investigator to be possibly or probably related to andexanet were ischemic stroke (3 patients; 0.9%), and DVT, myocardial infarction (MI), cerebral infarction, cerebrovascular accident, and PE (2 patients each; 0.6%).

There have been 54 deaths (15.3%) prior to the Day 30 visit; of these, 37 were adjudicated as cardiovascular deaths and 12 as non-cardiovascular deaths. Overall, the mortality rate was consistent with the expected burden of AEs in this patient population given the vascular risk factors, overall high morbidity, and poor prognosis of patients with acute major bleeding.

A total of 34 patients (9.7%) with any bleeding type experienced an adjudicated clinical thrombotic event (TE). While re-anticoagulation rates were similar between patients with and without TEs, the time to resumption of anticoagulation was markedly greater in patients with TEs.

No clinically meaningful changes in laboratory values related to andexanet (including hematocrit and hemoglobin) were detected in the study. Similarly, no clinically significant changes in vital signs and/or physical examination findings have been observed. Twenty patients (5.7%) had confirmed positive results for anti-andexanet antibodies after treatment. The titers were nearly all low values with no neutralizing activity in any patient samples.

A randomized clinical trial (Study 18-513, ANNEXA-I) is currently underway to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage.

2.0 STUDY OBJECTIVES

In patients requiring urgent surgery who are being treated with a direct or indirect FXa inhibitor, the objectives of this study are described in the subsections that follow.

2.1. Primary Objectives

- To evaluate the hemostatic efficacy following andexanet treatment.

2.2. Secondary Efficacy Objectives

- To evaluate the effect of andexanet on anti-fXa activity.

2.3. Exploratory Efficacy Objectives

- To evaluate the effect of andexanet on TG.
- To evaluate the use of red blood cell (RBC) transfusions.
- To evaluate the use of non-RBC, non-platelet blood products, and hemostatic agents.
- To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir.
- To evaluate the time from obtaining informed consent (study consent) to the start of surgery.
- To evaluate observed intraoperative blood loss and the difference between predicted versus observed blood loss.
- To evaluate the length of index hospitalization, intensive care unit (ICU) stay, time in a post-anesthesia care unit (PACU), time in the operating room (OR), and length of surgery.
- To evaluate the occurrence of re-hospitalization.
- To evaluate the occurrence of major post-surgical bleeding, including surgical wound hematomas.
- To evaluate the occurrence of re-operations for bleeding.
- To evaluate the effect of andexanet on TFPI.
- In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity.

2.4. Safety Objectives

- To evaluate the overall safety of andexanet, including AEs, SAEs, vital signs, physical examinations, clinical laboratory measurements, thrombotic events (TEs), mortality, and immunogenicity.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a Phase 2 multicenter, prospective, open-label, proof-of-concept study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery (must occur within 12 hours of consent) who have, within 15 hours prior to surgery, received 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. The start of surgery must be within 15 hours following the last dose of FXa inhibitor. If the time from last dose of FXa inhibitor is unknown or greater than 15 hours, patients with a local anti-fXa activity level obtained within 2 hours prior to consent > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin) may be enrolled. Patients enrolled in this manner should receive a high-andexanet dosing regimen. In such cases, the start of surgery must begin no greater than 4 hours after the blood collection for the local test. The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have sufficiently high anti-fXa activity levels.

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

The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the surgeon's assessment of intraoperative hemostasis using a pre-specified 4-point scale (Section 11.5.1) and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC).

In addition to hemostatic efficacy, the EAC will adjudicate all deaths, TEs, and post-surgical major bleeding events (e.g., surgical hematomas). The EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data approximately every 6 months.

In addition to the efficacy and safety objectives and endpoints, information obtained from this study is expected to include dosing considerations (adequacy of dosing and duration of dosing required) that will be used to inform a subsequent randomized Phase 3 trial for registrational purposes.

All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. The study schedule of activities can be found in Appendix A.

3.2. Blinding and Randomization

3.2.1. Randomization

There is no randomization in this study. All eligible patients will be enrolled and receive open-label andexanet treatment.

3.2.2. Blinding

This study will be open-label. However, the EAC will be blinded to all anti-fXa levels.

3.3. Duration of Study

The duration of the study for any individual patient will be up to 37 days.

There are 4 study periods. Study periods in the study for the respective cohorts are defined as follows:

- Screening Period: Day 1.
- Pre-surgical Assessment Period: Day 1.
- Treatment Period: Day 1.
    - Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~ 2.5 hours) but no greater than a total of 6 hours (including both the initial regimen and the extended infusion).
    - Re-dosing (low dose bolus and infusion) may occur within 12 hours after completion of the first course of andexanet treatment if protocol specified criteria are met, at the investigators discretion. [refer to Section 6.2]).
- Safety Follow-up Period: Days 1–30 + 7.

3.4. Discussion of Study Design, Including Choice of Control

3.4.1. Study Population

The study will enroll patients between the ages of 18 and 85 years who have recently taken an FXa inhibitor within 15 hours prior to start of surgery and who require urgent surgery for which reversal of anti-fXa activity is judged necessary.

If the time from last dose is unknown or greater than 15 hours, the patient may be enrolled provided a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin]). In such cases the start of surgery must be no greater than 4 hours after the blood collection time for the local test.

Patients who are in need of urgent surgery within 12 hours of consent may be enrolled. Patients undergoing procedures for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low are not eligible. Patients with life-threatening bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition, see Section 4.2) are also not eligible.

It is expected that eligible procedures may have varying degrees of tissue trauma but still have clinically relevant bleeding risk for which the reversal of FXa inhibition is judged necessary. For example, surgeries in a confined space (e.g., spinal cord decompression) can be considered to be at high bleeding risk even with relatively little tissue trauma, as opposed to an intra-abdominal surgery. Anticipated surgery types may include, but are not limited to, abdominal, thoracic, orthopedic, gynecological open and laparoscopic surgery. To ensure an adequate number of patients with certain key surgery types, abdominal surgeries (including both open and laparoscopic) and orthopedic surgeries will each comprise approximately 20% of the enrolled population. Patients undergoing only non-surgical invasive procedures (e.g., skin biopsies, lumbar puncture, cardiac catheterization, ERCP) will be excluded.

To align with previous studies of andexanet [4], the Efficacy Analysis Population for the study will only include patients whose central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin).

3.4.2. Rationale for the Study

The overall objective of the study is to gain direct insights regarding the efficacy and safety of andexanet in FXa-anticoagulated patients requiring urgent surgery. Additional information obtained from this study will include the adequacy and duration of andexanet dosing. The results of this study will be used to inform a subsequent randomized Phase 3 trial for registrational purposes.

3.4.2.1. Unmet Medical Need in Urgent Surgery

A substantial unmet medical need exists for patients taking FXa inhibitors who require rapid anticoagulant reversal prior to an urgent surgical procedure. In addition to the fact that approximately 1% of anticoagulated patients may require urgent surgery within 2 years of initiation [1, 2], management guidelines from the French Working Group of Perioperative Hemostasis suggest that 10% to 20% of treated patients may potentially undergo emergency surgery and invasive procedures during their lifetime [6]. Given the increasing adoption of FXa inhibitors worldwide, it is likely that progressively greater numbers of patients treated with FXa

inhibitors in need of urgent surgery will require reversal of anticoagulation, in addition to those with life-threatening or uncontrolled bleeding.

In general, it is well appreciated that urgent surgery is associated with an increased risk of complications as compared to elective surgeries. A recent study reported markedly increased rates of morbidity (12.3% vs. 6.7%) and mortality (2.3 vs. 0.4%) for urgent versus elective surgeries in 173,643 patients from a surgical database (NSQIP), of which 12% (> 20,000) were classified as urgent (non-elective/non-emergency) [7]. In the RE-LY study, the rate of major bleeding in dabigatran-treated patients was 17% for urgent surgery as compared to 3% in the larger study population. Perioperative rates of thromboembolism, major bleeding, and mortality were 5- to 10-fold higher in patients having an urgent rather than elective surgery/procedure. The need for urgent surgery was the strongest predictor of thromboembolism and major bleeding [8]. Similarly, data on 863 surgical patients treated with novel oral anticoagulants (NOACs) in the Dresden NOAC registry indicate an increase in major bleeding for patients with major versus minor surgery [9]. Finally, a sub-analysis of the Phase 3 ARISTOTLE trial showed a higher rate (4.9%) of major bleeding in apixaban-treated patients undergoing emergent surgery versus a rate of 2.1% in apixaban-treated patients in the overall study population [10, 11].

3.4.2.2. Management of Patients Taking FXa Inhibitors Requiring Urgent Surgery

There is currently no specific or approved treatment option for patients requiring reversal of FXa inhibition for urgent surgery. In general, if a patient is anticoagulated and requires surgery, the primary approach to managing this clinical scenario is to delay the procedure to facilitate elimination of the FXa inhibitor. Current practice is to weigh the risk of proceeding with the surgery, with the attendant prospect of hemorrhage, against the risk of delaying the procedure to achieve lower anti fXa activity levels. Inappropriate surgical delay could potentially result in serious or life-threatening clinical complications such as progressive contamination of the abdominal cavity (e.g., perforation of duodenal ulcer, perforated diverticulitis) or inflamed organ perforation (appendicitis). Postponement of treatment may also result in soft tissue infection progression, especially when diabetic comorbidity is present (e.g., abscess, necrotizing fasciitis). Delayed operative management for ischemic conditions could result in necrosis, prolonged postoperative management, and mortality.

Of relevance, additional studies have reported clinical outcomes such as mortality, complications, and increased use of health care resources associated with delays in surgical intervention [12]. In a recent cohort study evaluating patients with perforated peptic ulcers, every hour of delay from admission to surgery was associated with an adjusted 2.4% decreased probability of survival compared with the previous hour [13]. Conditions such as cholecystitis progressing to perforation, or ischemic consequences for small bowel obstruction are additional examples of surgical delay leading to clinical deterioration and requirements for more extensive operative management. Patients taking FXa inhibitors may experience delays in orthopedic procedures such as hip fracture repair, a procedure in which delay is proven to have adverse

clinical consequences [14]. While there is some variability (at least partially procedure-dependent) in the magnitude of delay associated with increased morbidity and mortality, it is generally accepted that the delay itself meaningfully increases the risk of a negative outcome.

If delaying the surgery is not an option, as is expected for most urgent surgeries, intraoperative management of bleeding complications may consist of hemodynamic support (e.g., fluid/volume replacement, RBC transfusion), use of hemostatic agents (e.g., tranexamic acid) and/or administration of coagulation factor products such as fresh frozen plasma (FFP)/platelet concentrates, recombinant factor VIIa (rfVIIa), factor eight inhibitor bypassing activity, and 3- and 4-factor prothrombin complex concentrates (PCCs) [15]. In general, published guidelines do not recommend the use of nonspecific agents such as PCC for preventative use in the absence of bleeding [16-18].

Though these agents (particularly PCCs) have not been approved by any regulatory agency for use in patients taking FXa inhibitors, they have nevertheless become used as a de facto standard of care for uncontrolled bleeding in patients treated with FXa inhibitors. That said, there is little mechanistic evidence supporting the use of PCCs as reversal agents for FXa inhibitors in any clinical context, including urgent surgery [19]. What clinical evidence exists consists primarily of healthy volunteer studies demonstrating increases in thrombin generation (albeit delayed), and inconclusive data on clinical readouts [20, 21]. Three case series have been published in patients treated with FXa inhibitors who were given PCCs prior to emergent/urgent surgery [22-24], but these were confounded by low numbers ([25], [10], and [24], respectively), poorly (or no) defined criteria for hemostatic efficacy, and relatively little (or no) effort to control for the time from last FXa inhibitor dose. Furthermore, high short-term mortality rates were also reported (29% and 51%, respectively). Taken together, the results cited above indicate that there is little to no evidence supporting the use of nonspecific coagulation factor products for prophylactic use to mitigate bleeding risk in FXa inhibitor-treated patients in need of urgent surgery.

Because of the inadequacy of the two therapeutic strategies discussed above (i.e., delaying surgery or non-specific coagulation factor replacement therapies), an unmet medical need remains for a specific, rapid reversal agent for patients in this clinical scenario. Andexanet has the potential to fill this unmet need.

3.4.3. Rationale for the Dose Regimen

All patients will receive 1 of 2 doses of andexanet based on the specific anticoagulant taken and timing of the last dose.

The andexanet dosing regimens to be examined in this study are as follows:

- Low dose: 400 mg IV bolus at a rate of 30 mg/min (duration of approximately 15 minutes) followed by a continuous infusion at a target rate of 4 mg/min for 120 minutes irrespective of the duration of surgery.

- High dose: 800 mg IV bolus at a rate of 30 mg/min (duration of approximately 30 minutes) followed by a continuous infusion at a target rate of 8 mg/min for 120 minutes irrespective of the duration of surgery.

Extended infusion at the low-dose (4 mg/min) may be administered for up to an additional 4 hours after initial dosing (bolus + infusion) is completed (1) in order to ensure mandatory continuous infusion from start to end of surgery, and (2) may continue into the immediate post-operative coverage per investigator discretion. Total dosing time (initial bolus + initial 120-minute infusion + any extended infusion) should be less than 6.5 hours.

Evidence to support this dosing regimen comes from PK/PD modeling that included results from the ANNEXA-4 study in bleeding patients. Data from the Phase 3 studies with apixaban and rivaroxaban, as well as a recently completed Phase 1 study of Generation 2 andexanet in healthy volunteers (Study 16-512-Direct Inhibitors; Section 1.4.3), confirm the levels of FXa inhibition and recovery of TG observed in the Phase 2 study. These doses of andexanet correspond to decreases in anti-fXa activity that correlate with normalization of hemostasis as measured by a TG assay. The change to the lower dose (400 mg) at 8 hours after the last administered FXa inhibitor dose was based on the PK-PD model that predicted the time at which equivalent anti-fXa activity reversal and TG normalization would be achieved.

In addition to the above, the doses for this study (19-515) were shown to substantially reduce anti-fXa activity and increase TG in a Phase 3b/4 study in which andexanet was given to patients receiving an FXa inhibitor who had acute major bleeding (ANNEXA-4).

3.4.4. Rationale for Extended Infusion or Re-Dosing of Andexanet

In this study, there is potential for patients to require additional andexanet treatment beyond what is initially stipulated (bolus + 120-minute infusion). For example, unpredictable events during surgery may prolong the duration of surgery. Based on clinical judgement of procedural or patient factors, the treating physician may determine that the infusion should additionally extend to the immediate postoperative period. In addition, a surgical patient may bleed after completion of surgery. Therefore, extended andexanet infusions (to address longer surgeries) and re-dosing of andexanet (for post-surgical bleeding events) will be implemented in the protocol.

A low-dose continuous infusion (4 mg/min) for up to an additional 4 hours was selected as the regimen to use for extended infusions, whereas a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes) will be used for re-dosing. The rationale for these dosing levels is based on the premise that the amount of reversal agent required to neutralize an FXa inhibitor diminishes as the inhibitor is eliminated over time.

Investigators will be required to document in the electronic case report form (eCRF) the clinical justification for why subjects require extended infusion of andexanet or additional dosing of andexanet during surgery. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for extended duration of dosing or re-dosing during surgery are outlined in Section 6.2.

3.4.4.1. Re-dosing Criteria

Factors that may determine if re-dosing is appropriate include the treating surgeon's consideration of patient factors, such as degree of visible bleeding, hemodynamic stability, need for hemostatic support products, or to avoid reoperation to control bleeding. The Investigator may also consider clinical suspicion that the patient has levels of FXa inhibition sufficient to contribute to bleeding based on patient factors such as time from last FXa inhibitor dose, safety assessments required by the protocol or routine care and renal function. Additionally, the need for re-operation to control bleeding may be considered reason re-dose to avoid the additional procedure.

3.5. Safety Plan and Monitoring

The study will be conducted in patients who are hospitalized. As such, treatment with andexanet and subsequent monitoring will be done in a medical setting. It is expected that patients requiring urgent surgery will remain hospitalized for at least 12 hours, the timeframe for the primary efficacy evaluations. During the first 12-hour period (Study Day 1), AEs, vital signs, physical examinations, and laboratory testing will be performed as indicated in Appendix A to monitor safety. Enrolled patients will be closely monitored during the period where they are most vulnerable and the risk of thrombosis is highest.

Survival status will be ascertained on Study Day 30, and, if applicable, cause of death will be recorded. Antibody samples will be taken at baseline and Day 30 to assess immunogenicity against andexanet, FX, FXa, nAb, and HCPs. Due to the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) pandemic, the Day 30 visit may be conducted by phone; considerations for laboratory samples are discussed in Section 3.7.

Of the 352 patients, 9.7% of patients with acute major bleeding in ANNEXA-4 experienced protocol-defined, adjudicated TEs that occurred within 30 days of andexanet treatment. While the attributability of these events to andexanet is uncertain, it is significantly possible that they will occur in the current study, given the anticipated enrolled population, for which reversal of anticoagulation may expose the underlying risk of TEs, and andexanet's known effects on coagulation biomarkers such as D-dimer, F1+2, and TFPI. In this study, patients with TEs within 30 days of Screening, those with a history of hypercoagulable states, and those who received procoagulant products within 7 days of Screening will not be eligible for the study due to their much greater risk for TEs in general and following anticoagulation reversal. In this study, TEs will be considered AEs of special interest (AESIs) and will be reported within 24 hours to the

Sponsor. Thrombotic events, both suspected and confirmed by adjudication, will be tracked as safety endpoints for the study. To mitigate the risk of TEs, Investigators are encouraged to consider resumption of an anti-thrombotic agent (preferably oral) as soon as it is clinically appropriate. Additional clinical precautions to mitigate thrombotic risk in postoperative care such as early mobilization, sequential compression devices or other routine measures should also be strongly considered.

Prior and ongoing clinical studies have identified infusion reactions of mild or moderate intensity as an AE related to administration of andexanet (described in Section 1.4.5). Patients in this study will receive andexanet in an inpatient, monitored setting under medical supervision and immediate access to resuscitative measures. Infusion reactions observed in prior and ongoing studies have had their onset during the infusion itself.

Whether or not patients have been discharged from the hospital, they will undergo the Study Day 2, Study Day 3, and Follow-up Day 30 visits to assess safety. Due to the theoretical possibility of antibody formation to andexanet, FX, FXa, or HCPs, antibody testing will be performed at baseline and at the Study Day 30 visit (see Section 3.7 for modifications due to COVID-19 guidelines).

The independent EAC, in addition to adjudicating the primary endpoint, will also adjudicate all TEs, deaths, and all post-surgical bleeding events using pre-defined criteria as described in their charter. A DSMB will review all safety data approximately every 6 months and will be empowered to recommend modifying or stopping the trial for safety reasons if warranted. In addition, safety data will be reviewed by the Sponsor at an ongoing basis. Guidelines for the management of specific AEs and intraoperative rescue strategies are provided in Section 8.0.

3.6. Benefit and Risk Assessment

Factor Xa inhibitors are a significant therapeutic advance in several indications. However, a significant risk of anticoagulation with FXa inhibitors is the potential for uncontrolled bleeding. In the case of urgent surgery, a delay in surgical treatment necessary to sufficiently diminish anti-coagulant concentrations could potentially result in deleterious clinical consequences. At least 1 report has suggested that a delay greater than 12 hours increases the risk of a perforation [26]. In hip fracture surgery, a delay greater than 24 hours is well known to be associated with mortality [27]. Furthermore, other studies suggest that a delay greater than 12 hours leads to an increased risk of in-hospital pneumonia [28] and mortality [29]. Given the above data, at least 1 academic society has issued guidance to classify urgent surgeries as those that can be delayed no longer than 12 hours [30]. Taken together, the above data support a 12-hour threshold for defining urgent surgery. The 15-hour cutoff for the time from last FXa inhibitor dose was implemented based on evidence from the ANNEXA-4 study, in which the percentage of enrolled patients with a baseline anti-fXa activity < 75 did not differ substantially between time from last dose cutoffs of 12 and 15 hours.

While andexanet is approved for the management of acute major bleeding related to FXa inhibitor use, it is unknown whether it is efficacious and safe in patients who require urgent surgery in the setting of recent use of an FXa inhibitor. Andexanet may be beneficial in reversing anticoagulation due to FXa inhibition and, thus, facilitating normal hemostasis during the surgical procedure. In addition to any personal benefit to individual patients, there is a potential benefit to all current and future patients treated with andexanet (and, more generally, all patients taking FXa inhibitors) from the insights gained through this clinical study.

The risks of study participation involve the risk of experiencing an AE related to andexanet or to the study procedures. To date, no major safety issues directly attributable to andexanet have definitively emerged in clinical studies. However, whenever chronic anticoagulation is reversed in patients with an indication to receive it, the risk of thromboembolic events is increased. Additionally, surgical intervention can also increase thromboembolic risk. This risk must be balanced against the potential for new or worsening bleeding related to the surgery. The PD effect of andexanet is short. Therefore, shortly after the infusion is discontinued and once the potential for bleeding is minimized, it will be possible to return the patient to a therapeutically anticoagulated state as needed. It is recommended that the Investigator carefully weigh the risk of new bleeding against the risk of thrombosis when considering when to resume anticoagulation for the patient.

Procedural risks inherent to the urgent surgical procedure itself would vary based on the procedure type and individual patient risk factors, and should be additionally communicated to the patient by the treating physician.

The safety monitoring plan for this study is robust (see Section 3.5), including treatment of patients in a hospital setting, an approximate 30-day safety follow-up, ongoing review of safety data by the Sponsor and independent safety reviews by the DSMB as well as adjudication of TEs, deaths, hemostatic efficacy, and post-surgical bleeding events by the EAC.

Based on the above considerations, the potential risks to patients in this study are justifiable. Patients or their legally authorized representative will be consented as to the potential risks and will be required to sign an informed consent form (ICF), documenting their understanding of these risks and willingness to participate in the study.

3.7. Acknowledgement of Benefit: Risk During COVID-19 Pandemic

The Sponsor takes note of the ongoing COVID-19 pandemic and its potential impact on planned and ongoing clinical trials. In accordance with recent guidance from various regulatory agencies such as the FDA, European Medicines Agency (EMA), and Medicines and Healthcare products Regulatory Agency, we recognize that current challenges due to the pandemic may lead to changes in the operational conduct of the study as well as the benefit:risk of participation in subjects infected with COVID-19.

We have taken these factors into consideration as applied to Study 19-515 (ANNEXA-S; Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Require Urgent Surgery). Key safety parameters to be evaluated in this study include the occurrence of TEs at 30 days, given that the target population of the study is characterized by a high background thrombotic risk.

As patients who require urgent surgery in this study will be hospitalized for at least 12 hours (possibly longer), and may be in an intensive care setting, it is conceivable that study participants could be at risk for nosocomial transmission of COVID-19. While current understanding of the pathophysiology of COVID-19 infection continues to evolve rapidly, recent anecdotal reports have suggested that COVID-19 may lead to a pro-thrombotic state in certain individuals. As such, consideration should be given toward the possibility that COVID-19 will increase thrombotic risk in ANNEXA-S enrollees.

That said, while COVID-19 may lead to a pro-thrombotic state, there is no mechanistic basis to conclude that it specifically targets patients receiving andexanet, or preferentially increases thrombotic risk in patients treated with andexanet relative to those receiving usual care.

Importantly, given the level of uncertainty with this risk, we believe it will be prudent to monitor the frequency of TEs on an ongoing basis as the study progresses. Investigators will be issued guidance discussing COVID-19 and its putative pro-thrombotic effect. Within this guidance, Investigators will be asked to maintain vigilance for potential TEs and to promptly report them should they be clinically suspected. Fortunately, monitoring is already in place, as TEs are designated as AESIs in the protocol, and the DSMB is tasked with evaluating safety data on a continuing basis. Within the protocol, Investigators are asked to monitor for TEs and submit them for adjudication when they occur. Furthermore, Investigators are encouraged to reinitiate anticoagulation as soon as medically warranted to prevent thrombosis.

Finally, as FDA and EMA COVID-19 guidelines encourage reducing nonessential study visits, the Day 30 visit may be conducted by phone, and the sample collection for nAb evaluations at Day 30 are optional. Additional laboratory sampling indicated for the Day 30 visit (Appendix A) may be conducted at follow-up visits per the standard of care to minimize nonessential study visits.

In summary, early reports have suggested that COVID-19 infection may be associated with a pro-thrombotic state. Measures have been implemented to monitor for TEs in the study.

4.0 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1. Inclusion Criteria

All of the following criteria must be met for the patient to be eligible to participate in the study:

1. Either the patient or his or her medical proxy (or legal designee) has given written informed consent prior to Screening.
2. Age ≥ 18 and < 85 years old.
3. Requires urgent surgical intervention that must occur within 12 hours of consent, for which reversal of anti-fXa activity is judged necessary.
4. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], edoxaban [last dose 30 mg or greater] or enoxaparin [≥ 1 mg/kg/d]):
   a. ≤ 15 hours prior to start of surgery.
   b. > 15 hours prior to start of surgery or unknown time from the last dose, if documented anti fXa activity is > 100 ng/mL (> 0.5 IU/mL for enoxaparin, or over the equivalent IU/mL threshold on a low molecular weight heparin assay; see Laboratory Manual) within 2 hours prior to consent. Note: Patients enrolled in this manner should receive a high-andexanet dosing regimen.
5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential).
6. Willingness to use highly effective methods of contraception [31] through 30 days following study drug dose (for female and male patients who are fertile).

4.2. Exclusion Criteria

If a patient meets any of the following criteria, he or she is *not* eligible to participate:

1. Surgery for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low.
2. Acute life-threatening bleeding (ISTH criteria [32]) at the time of Screening:
   a. The patient has acute-overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained.
   b. The patient has overt bleeding associated with a fall in hemoglobin level by ≥ 2g/dL, OR, a hemoglobin ≤ 8 g/dL if no baseline hemoglobin is available.
   c. The patient has acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal.

3. Any surgical procedure that involves the intraoperative use of systemic, intravascular, unfractionated heparin.
4. Primary procedure being considered for efficacy evaluation is a non-surgical interventional procedure (e.g, skin biopsy, lumbar puncture, cardiac catheterization, endoscopic retrograde cholangio-pancreatography).
5. Expected survival of < 1 month due to comorbidity.
6. Known "Do Not Resuscitate" order or similar advanced directive.
7. The patient has a recent history (within 30 days prior to Screening) of a diagnosed TE as follows: VTE (including DVT, PE, intracardiac thrombus); MI (including asymptomatic troponin elevations); disseminated intravascular coagulation (DIC); acute traumatic coagulopathy; cerebrovascular accident; transient ischemic attack; unstable angina pectoris hospitalization; or severe peripheral vascular disease (see Appendix B for DIC scoring algorithm).
8. Acute decompensated heart failure or cardiogenic shock at the time of screening (see Appendix C for cardiogenic shock definition).
9. The patient has sepsis or septic or hemorrhagic shock at the time of Screening (see definition in Appendix C).
10. The patient has heparin-induced thrombocytopenia (with or without thrombosis).
11. Inherited coagulopathy (e.g., anti-phospholipid antibody syndrome, protein C/S deficiency, Factor V Leiden) at time of Screening.
12. Platelet count < 80,000/μL at the time of Screening.
13. Last dose of apixaban < 2.5 mg, rivaroxaban < 10 mg, edoxaban < 30 mg, enoxaparin < 40 mg.
14. The patient is pregnant or a lactating female.
15. The patient has received any of the following drugs or blood products within 7 days of enrollment:
    - Vitamin K antagonists (e.g., warfarin).
    - Dabigatran.
    - PCC products (e.g., Kcentra®), rfVIIa (e.g., NovoSeven®).
    - Whole blood, plasma fractions.
    - Note: Administration of tranexamic acid (TXA), platelets, or packed red blood cells (PRBCs) is not an exclusion criterion.
16. The patient was treated with an investigational drug < 30 days prior to Screening.
17. Prior treatment with andexanet.
18. Known hypersensitivity to any component of andexanet.

19. Known allergic reaction to hamster proteins.
20. Known or suspected (i.e., presumed positive) COVID-19-related illness at the time of Screening.

4.3. Criteria for Discontinuation from the Study

A patient may elect to discontinue participation in the study at any time. However, all efforts must be made to follow patients for the full duration of the study and to encourage all patients to complete the Day 30 contact.

This study will be conducted in such a way as to minimize patients that withdraw consent. The following points will apply:

- Patients who discontinue study treatment or some procedures should not be discontinued from the study. Investigators must distinguish the difference between patients who discontinue study drug or procedures from those who withdraw consent and do not intend to participate further in the study follow-up visits or contacts (withdrawers).
- All Investigators must commit to minimizing the number of patients who do not complete the study.
- If patients cannot or will not return for visits, the Investigator (or their designee) should attempt to contact them by telephone or other means.

Reasons for all study withdrawals will be recorded in the eCRF.

4.4. Criteria for Discontinuation of Andexanet

Andexanet may be prematurely discontinued for a number of reasons, including:

- Any intolerable AE that cannot be ameliorated by appropriate medical intervention or that in the opinion of the Medical Monitor or Investigator would lead to undue risk if the patient were to continue on treatment.

Patients who discontinue study drug may still continue in the study. Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, in which case they should undergo an Early Termination visit (complete the same procedures as Day 30 Visit).

Reasons for all discontinuations of andexanet will be recorded in the eCRF.

4.5. Patient Replacement

Patients who discontinue prematurely will not be replaced.

4.6. Study Completion

Study completion for each patient is defined as completion of the Day 30 visit or, at a minimum, the time at which Day 30 mortality data are recorded. The Sponsor defines the end of the trial as "the last visit for the last patient undergoing the trial."

In certain European Union (EU) Member States, "study completion" may also be considered the same as "end of trial."

5.0 ENROLLMENT AND STUDY PROCEDURES

A summary of the patient visits and clinical evaluations can be found in Appendix A. Details on efficacy and safety assessments can be found in Section 10.0. Laboratory assessments, clinical assessments, and/or procedures performed per Investigator or institutional standard of care at presentation, but before signing of informed consent, may be used to fulfill protocol requirements.

5.1. Screening Period

Patients will be identified by their need for urgent surgery that cannot be delayed and time from last dose of an FXa inhibitor. Informed consent will be administered followed by assignment of a patient identification number. Eligibility will be assessed by completion of demographics, medical history, physical examination, determination of last time of anticoagulated dose or plasma level. Baseline safety assessment will be performed inclusive of vital signs and weight, collection of local clinical laboratory results. Baseline efficacy and safety labs will be collected for analysis by a central laboratory. Following execution of the informed consent, changes in patient status that meet the definition of AEs will be recorded (Section 9.0).

5.2. Visit Procedures (Days 1, 2, 3, and 30)

5.2.1. Day 1 Inpatient

On Day 1, patients will receive treatment with andexanet and will undergo the urgent surgery. Prior to start of dosing, patients will have the general health status assessed and categorized according to the American Society of Anesthesiologists Classification, repeat safety assessments (serial vital signs, repeat physical examination, and local labs). Study specific assessments and central laboratory samples will be collected to assess *in vitro* hemostasis.

The dose of andexanet will be selected based on anticoagulant product/brand, dose, and time of last dose of anticoagulant the patient is taking. The duration of the surgery will determine the total dose and duration of andexanet administered. Generally, it is planned for patients to complete the bolus and start the infusion immediately prior to the start of surgery and to receive andexanet infusion, including extended dosing as necessary, for the duration of their surgical procedure. During the surgery, the investigator and staff will provide assessment of hemostasis and record all supporting medications related to hemostasis support. Patients should remain hospitalized on Day 1. The patient will be scheduled for study Day 2 visit.

5.2.2. Day 2 and Day 3

Follow-up visits on Days 2 and 3 will be conducted as an inpatient or outpatient. Patients will receive safety assessments (vital signs, physical examination, and local laboratory testing) along with collection of samples for central laboratory analysis to assess hemostasis. Diagnostic and therapeutic products supporting hemostasis will be assessed, documented, and reported. Adverse events and concomitant medications will be recorded. The patient will be scheduled for study Day 30 visit.

5.2.3. Day 30

The Follow-up visit on Day 30 will be conducted as an inpatient or outpatient, and the mortality status check along with concomitant medications and AEs can be conducted by phone; for considerations and modifications during ongoing COVID-19 pandemic, see Section 3.7). Safety assessments will be performed (vital signs, physical examination, weight, and local laboratory testing) along with collection of samples for central laboratory analysis to assess immunogenicity and hemostasis. Adverse events and concomitant medications will be recorded. The investigator will assess and report duration of hospitalization by unit type (emergency, critical care units, post-op units, etc.) and document the survival status of the patient.

Procedures performed at the Day 30 visit will be also performed for all early terminating patients (Section 5.4).

5.3. Unscheduled Visit

During the study, additional clinical visits may be scheduled at the Investigator's discretion in order to care for the patient. The reason for an unscheduled visit will be recorded in the eCRF.

The following must be performed at an unscheduled visit:

- Record the reason for the unscheduled visit.
- Record AEs since last study visit.
- Record use of concomitant medication since last study visit.

Additional procedures may be performed at an unscheduled visit as deemed necessary by the Investigator. These may include any of the central or local laboratory testing done at scheduled visits, vital signs, additional evaluations for bleeding, or assessment of AEs. Record study specified procedures and data captured as unscheduled visits.

5.4. Early Termination Visit

An Early Termination visit will be conducted if the patient discontinues from the study before the Follow-up Day 30 visit. In addition to the Day 30 procedures outlined in Section 5.2, the following procedures will be performed at the ET visit:

- Record the reason for early termination.
- Record dates of use of anticoagulant(s) on the anticoagulant eCRF.
- Perform a final assessment of bleeding.

Vital signs and local laboratory assessments for complete blood count (CBC) should also be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.

6.0 DRUG SUPPLIES AND DOSING

6.1. Formulation

Andexanet alfa (PRT064445) is a lyophilized product for reconstitution for IV injection that is supplied by the Sponsor. It is supplied in single-use, type I glass vials with grey rubber stoppers and flip-off seals at a concentration of 200 mg/vial. The composition in each vial is listed in Table 1. Following reconstitution with Sterile Water for Injection, the concentration of the reconstituted solution is 10 mg/mL. The lyophilized product must be reconstituted using Sterile Water for Injection before use. For details on reconstituting/ preparing andexanet, please refer to the Pharmacy Manual.

Table 1: Reconstitution Volumes and Composition for Andexanet for Injection

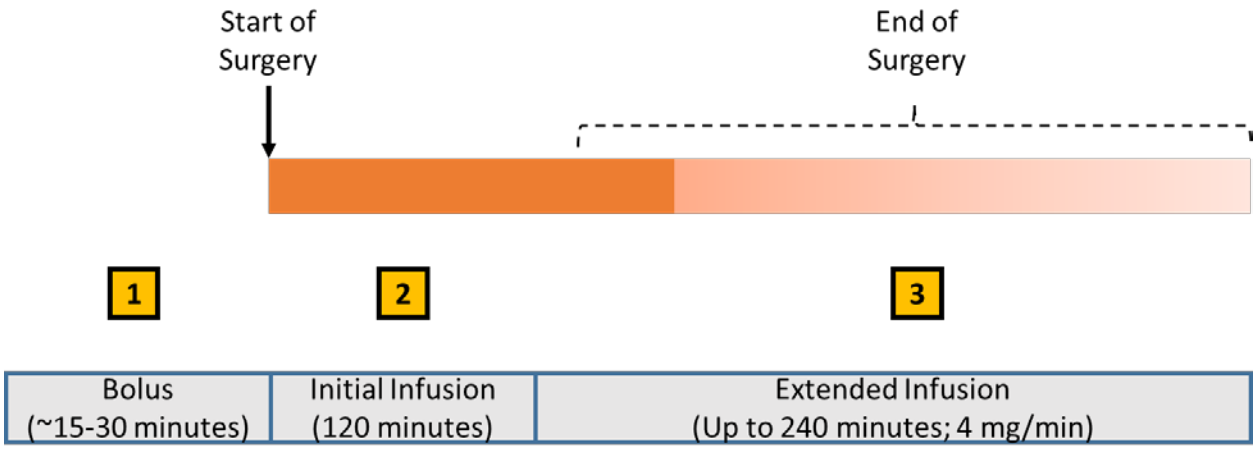
Vial Contents	**200 mg Vial**
Reconstitution Volume	**20.0 mL SWFI**
Ingredients	***Quantity per Vial***
Andexanet (PRT064445)	200 mg
Tris (Tromethamine)	6.52 mg
Tris HCl	7.33 mg
L-Arginine Hydrochloride	94.8 mg
Sucrose	200 mg
Mannitol	500 mg
Polysorbate 80	2.0 mg
Sterile Water for Injection	QS to 20 mL (removed during lyophilization process)

HCl = hydrochloride; QS = Quantity sufficient; SWFI = Sterile water for injection

6.2. Dosing and Administration

The timing of andexanet dosing in relation to the surgical procedure is depicted schematically in Figure 3.

Figure 3: Schema for Andexanet Dosing



(1) Bolus to be completed prior to start of surgery
(2) Initial infusion for at least 120 minutes, and from start to end of surgery
(3) Extended 4 mg/min infusion for up to 4 hours

Key Dosing Directives:

- Initial Bolus (low/high-dose) must be completed prior to start of surgery (initial skin incision).
- Initial dosing (low/high-dose bolus + 120-min infusion) should be completely administered irrespective of surgery length.
- Infusion should continue throughout the duration of surgery, defined as skin incision to skin closure (or equivalent milestone if skin closure is not completed intentionally).
- Extended infusion (up to 4 hours at 4 mg/min) (1) may be administered to ensure continuous infusion to match the duration of the surgery, and (2) can additionally proceed into the immediate postoperative period per investigator discretion.

Initial Dosing (Bolus + 2-hour infusion):

The initial andexanet dosing regimen will consist of the following:

1. An IV bolus, (to be completed prior to surgery)
   followed immediately by
2. An IV continuous infusion lasting for at least 120 minutes, (irrespective of the duration of surgery).

The bolus should be initiated not more than 30 minutes before, and must be completed by, the start of surgery (i.e., at the first incision). The bolus will be followed immediately by a continuous infusion lasting at least 120 minutes, irrespective of the length of the surgery. It is possible that the infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens (Table 2).

If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes). Note that the surgeon's assessment of intraoperative hemostasis is to occur at the end of surgery, irrespective of the total duration of andexanet infusion.

Extended Infusion (maximum of 4 additional hours at 4 mg/min)

Extended Infusion may be administered after completion of initial dose (bolus + 2-hour infusion):

1. To ensure continuous intraoperative infusion lasts the duration of the surgery**, (**if initial 2-hour infusion is completed prior to end of surgery)
   and
2. To provide coverage during the immediate postoperative period, per investigator clinical judgement.

If the initial andexanet dosing regimen (bolus plus 2-hour infusion) is completed **prior** to the end of the procedure, the infusion should continue at a low dose (only 4 mg/min) at least through the end of the surgery (skin closure or equivalent milestone).

Extended infusion may also continue after the end of surgery per investigator clinical judgement if deemed appropriate for the immediate post-operative period.

To facilitate the extended infusion, approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

Allowable Total Length of Dosing (Initial + Extended = up to 6.5 hours):

The total length of the initial dosing duration of andexanet (initial infusion plus extended infusion) should last no longer than 6.5 hours. Total study drug administration greater than 6.5 hours, while not prohibited, is strongly discouraged.

Re-dosing:

If a post-operative patient meets the applicable criteria for andexanet re-dosing (Table 2), he/she may be re-dosed. All patients that are re-dosed will be administered a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes). If a patient is re-dosed, a baseline anti-fXa activity sample will be drawn beforehand for central laboratory analysis; no post-initiation anti-fXa activity will be analyzed via local laboratory.

Table 2: Andexanet Dosing Paradigm and Criteria for Extended Treatment or Re-Dosing

Dose	Timing of Last Dose of FXa Inhibitor	Initial IV Bolus	Follow-On IV Infusion	Extended Infusion
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban 10 mg • Apixaban 2.5-5 mg • Enoxaparin 40 mg • Edoxaban 30 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes (480 mg total) irrespective of the duration of surgery	The infusion may be extended beyond 120 minutes at a rate of 4 mg/min (low-dose) for up to 4 additional hours.
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **> 15 hours or unknown time** • Local anti-fXa > 100 ng/mL (0.5 IU/mL for enoxaparin)	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes (960 mg total) irrespective of the duration of surgery	
a. Initial Bolus must be completed prior to start of surgery (initial skin incision). b. Initial dosing (bolus + 120 min infusion) should be completely administered regardless of surgery length. c. Infusion should continue throughout the duration of surgery, (defined as skin incision to skin closure or equivalent milestone).				
Criteria for Extended Infusion				
Extended Infusion (4 mg/min only) may continue up to an additional 4 hours to ensure continuous intraoperative infusion for the duration of surgery. The infusion may also continue through the immediate postoperative period at the Investigator's discretion.				

Criteria for Re-Dosing with Andexanet
Consider re-dosing with andexanet (400 mg bolus + 4 mg/min infusion for 120 min) only if: a. New, clinically significant, surgery-related, post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b. The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c. Re-dosing initiation occurs within 12 hours after the completion of the surgical procedure.

FXa = Activated factor X; IV = Intravenous.

6.3. Storage

The labeled storage condition for andexanet is refrigerated, (i.e., 2-8°C). The temperature of the medicine refrigerator should be monitored with an electronic temperature monitoring device.

6.4. Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write at least the date dispensed, dose dispensed, lot or batch code, person dispensing, and the patient's identification number on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record.

All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to the Sponsor or its designee only after written authorization is obtained from the Sponsor or its designees. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 13.5.

7.0 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1. Prior Medications and Treatments

See Section 4.1 and Section 4.2 for restrictions on prior medications and treatments.

7.2. Concomitant Medications and Procedures, Hemostatic, and Procoagulant Treatments

7.2.1. Anticoagulants and Antiplatelet Drugs

Investigators may choose to re-start anticoagulants or antiplatelet drugs (including, but not limited to prasugrel, ticagrelor, clopidogrel, aspirin, and non-steroidal anti-inflammatory drugs) at any time based on clinical judgment. If anticoagulants or antiplatelet agents are restarted during the study, the date, time, dose, and agent(s) used should be recorded on the eCRFs. Heparin-based products deemed to be necessary per the Investigator's judgement (such as for postoperative DVT prophylaxis) may be started at any time. However, it should be noted that any agent with anti-fXa properties may be suboptimally effective when administered within 1 hour after cessation of andexanet infusion, as this time interval represents the effective $t_{½}$ of the drug.

7.2.2. Blood Products

To maintain uniformity in transfusion practices across study participants, it is strongly suggested that the trigger for PRBC transfusion is hemoglobin ≤ 8.0 g/dL (± 1 g/dL). The hemoglobin triggering a transfusion, clinical stability factors (e.g., shock) influencing the decision to transfuse, as well as the number of units transfused should be recorded on the eCRFs.

Whole blood and platelet transfusions may be administered according to standard institutional/local practices and/or guidelines. Investigators may consider using pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) per their judgement in case of hemodynamic necessity. Otherwise, treatment with the above products is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of procoagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) and whole blood intraoperatively will result in the patient being considered having poor hemostatic efficacy (see Table 3) with andexanet.

Use of blood products, including number of units transfused and the date and time of administration should be recorded on the eCRFs.

7.2.3. Hemostatic Agents

Investigators may consider using systemic anti-fibrinolytic (e.g., aminocaproic acid and TXA) and other systemic hemostatic agents if a patient is found to require further hemodynamic support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Similarly, local hemostatic agents (e.g., microfibrillar collagen and chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) may be used if a patient is found to require further hemodynamic support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of hemostatic agents, their dose, and the date and time of administration should be recorded on the eCRFs.

7.2.4. Concomitant Procedures

During this study, patients will not be permitted to participate in any other trial that would involve a drug or a medical device during the 30- to 37-day Follow-up period. However, the patient will be permitted to participate in non-interventional trials.

7.3. Post-Surgical Bleeding and Rescue Therapy

In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated during surgery, due to post-surgical bleeding events.

Investigators will therefore be allowed to deliver a second dose (i.e., re-dose) of andexanet (low-dose bolus of 400 mg + 120-minute continuous infusion of 4 mg/min only) as rescue therapy should such a situation arise. If re-dosing is deemed necessary, Investigators will be required to document in the eCRF the clinical justification for why subjects require additional dosing of andexanet. Study procedures will mirror those required for the initial andexanet dosing. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for re-dosing are outlined in Section 6.2. If a patient is confirmed to have post-surgical bleeding by the EAC, then they will be considered to have poor hemostatic efficacy (irrespective of the treatment given for bleeding, if any).

In the event a patient continues or restarts bleeding even after re-dosing with andexanet (or does not meet the criteria for re-dosing), standard of care should be employed and appropriately captured on the eCRFs.

8.0 MANAGEMENT OF SPECIFIC ADVERSE EVENTS AND INTROAOPERATIVE RESCUE STRATEGIES

8.1. Infusion Reactions

As described in Section 1.4.6, mild to moderate infusion reactions have been reported in healthy subjects treated with andexanet. These infusion reactions have generally resolved without interruption of the infusion or medical intervention. In the event that the Investigator determines that intervention is warranted, consideration may be given to slowing the infusion rate, or temporary interruption of the dose followed by re-starting the infusion at a slower infusion rate. Treatment with diphenhydramine may also be considered.

8.2. Thrombotic Events

Patients will be monitored carefully for signs and symptoms of TEs (i.e., strokes, transient ischemic attacks, MIs, DVTs, PEs, arterial systemic embolisms) throughout the course of the study. Should a diagnosis of a TE be considered, it is expected that an appropriate evaluation will be performed (e.g., head computed tomography [CT]/magnetic resonance imaging [MRI], electrocardiogram [ECG]/cardiac enzymes, lower extremity ultrasound, pulmonary vascular imaging). Investigators are requested to consult the guidance listed in Appendix E when considering whether an event should be considered a TE and therefore be submitted for adjudication. All events submitted for adjudication will be formally considered a suspected TE. Both suspected TEs and TEs confirmed by adjudication will be monitored as safety endpoints.

8.3. Intraoperative Rescue Strategies

Regarding the intraoperative period, it is mandated that andexanet therapy will continue through the duration of the surgical procedure. If a procedure runs longer than the initial bolus and infusion dose of andexanet, the infusion should continue at a low rate (4 mg/min) until the conclusion of the surgery. No additional dosing of andexanet, such as a re-bolus, will be allowed during the procedure, even if bleeding should continue or recur (Section 6.2).

9.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

9.1. Safety Parameters and Definitions

9.1.1. Adverse Events

According to the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which may or may not have a causal relationship with the treatment.

An AE can be any of the following:

- Unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related.
- Any newly occurring event or exacerbation of previous condition (e.g., increase in severity or frequency) since the administration of study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

9.1.2. Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Is fatal (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening means that, in the opinion of the Investigator or Study Sponsor, the patient/subject was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother who was exposed to study drug or where the father was exposed to study drug before conception.
- Is an important medical event. An important medical event is an event that may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe MI); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on the strict regulatory definitions listed above and serves as a guide for defining regulatory reporting obligations. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted serious criteria. Thus, severity and seriousness need to be independently assessed for each AE recorded on the AE eCRF.

9.1.3. Non-Serious Adverse Events of Special Interest

The AESIs for this study include the following:

- A thrombotic or embolic event of any severity.

All AESIs, whether serious or non-serious, must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Non-serious AESIs must be entered on the AE eCRF with a check in the AESI box.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs (Section 9.1.1 for definition) are recorded on the AE eCRF and reported to the Sponsor in accordance with instructions provided in this section.

For each AE recorded on the AE eCRF, the Investigator will make an assessment of seriousness (Section 9.1.2), causality (Section 9.2.2), and severity (Section 9.2.3).

9.2.1. Adverse Event Reporting Period

To comply with regulatory requirements, all SAEs and non-serious AESIs, regardless of causality, that occur from the date of signing of the ICF until 30 days after the last study drug treatment, must be reported to the Sponsor or its safety designee within 24 hours from Investigator awareness of the event. Survival status and reason for death will be ascertained at the Follow-up Day 30 study visit.

Patients who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate eCRF through the Follow-up Day 30 visit.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported to the Sponsor or safety designee. These pre-dose AEs will be collected on the AE eCRF and assessed as not related to study drug, but will be assessed for relationship to study procedures/tests and interventions.

After initiation of study drug, all TEAEs, regardless of relationship to study drug, will be reported until **30 days after the last dose of study drug**. Any SAE that occurs with an onset date later than 30 days after completion of the study and that the Investigator considers to be related to study medication must be reported to the Sponsor or safety designee.

To report any SAEs, the SAE Report Form provided to the clinical study site must be completed with the available information. Non-serious AEs that are AESIs must be reported on the SAE form with the box for AESI checked. The information collected must include at minimum the following: patient number, study drug(s) received, the event term, the serious criteria met for the AE, a narrative description of the event, and an assessment by the Investigator of the severity/intensity of the event and relationship to study drug(s). The SAE report should be sent to the Sponsor or safety designee within 24 hours of Investigator awareness. Follow-up information on the SAE should be sent promptly by the Investigator to the Sponsor or safety designee when any additional relevant information about the SAE becomes known to the Investigator, or as requested by the Sponsor or safety designee. Safety reporting contact information is located in the Study Reference Manual.

The Sponsor will immediately notify the Investigator about important safety or toxicology information, including antibodies against FX or FXa identified in a patient treated with andexanet in any clinical study, as it becomes available. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) about new and relevant safety information regarding the study drug, including

serious adverse drug reactions involving risk to human subjects, in accordance with the applicable policies. Certain countries (e.g., the Netherlands), require the Sponsor to notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not listed by nature or severity in the Investigator's Brochure.

9.2.2. Assessment of Causal Relationship

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or re-introduction of study drug (as applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

The following categories should be used in the causality assessment of suspected adverse reactions:

Probable

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; and
- Was unlikely to have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Possible

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; but

- Could have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unlikely

The AE:

- Does not follow a reasonable temporal sequence from the time of study drug administration; and
- Was most likely produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated

- This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention other than bleeding control, or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality. Importantly, lack of efficacy does not necessarily constitute relatedness to study drug.

9.2.3. Assessment of Severity

The Investigator must determine the severity of the event according to the criteria below and the Investigator's clinical judgment. Severity describes the intensity of the AE.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living
Grade 4	Life-threatening consequence or urgent intervention indicated
Grade 5	Event resulted in death

9.2.4. Procedures for Recording AEs

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF. Avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in the event field on the AE eCRF.

All AEs spontaneously reported by the patient and/or in response to an open-ended question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate forms in the eCRF.

Only 1 AE term should be recorded in the event field on the AE eCRF. When possible, a unifying diagnosis, or signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as a "common cold" rather than listing each symptom separately.

9.2.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record tumor lysis syndrome rather than hypocalcemia, hyperkalemia, hyperuricemia, etc.). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.2.4.2. Adverse Events that are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

9.2.4.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE eCRF with the severity (intensity or grade) of the events recorded at the time the event is first reported.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs, or notes a change in severity or seriousness. Each recurrence of an AE should be recorded as a separate event on the AE eCRF. For example:

- If Grade 1 vomiting has worsened to Grade 2 five days after onset, the Grade 1 vomiting is resolved on the date when the severity changed, and Grade 2 vomiting is recorded as a new event on the eCRF with onset date reflecting the change in severity.

If non-serious event of neutropenia required hospitalization 5 days after onset, the event is resolved on the hospitalization date, and a new SAE of neutropenia is recorded on the eCRF with start date reflecting when the event required hospitalization.

9.2.4.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Is clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE eCRF.

9.2.4.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Is clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF (Section 9.2.4.3 provides details on recording persistent AEs).

9.2.4.6. Deaths

Death should be considered an outcome and not a distinct event. All deaths that occur during the protocol-defined AE period should be reported as SAEs, regardless of attribution to study drug. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept (e.g., septic shock) with a fatal outcome. When the event that led to death cannot be identified (e.g., death of unknown origin) report "unexplained death" as the AE and update it when new information clarifies the event that led to death. Only 1 AE can be reported with a fatal outcome for each patient who dies. Other AEs that continued up to time of death should be reported with an outcome of not recovered/resolved. In the event that the death is attributed solely to natural progression of the underlying bleeding, the event is not reportable and should not be recorded as an AE.

9.2.4.7. Preexisting Medical Conditions

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE form, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.2.4.8. Hospitalization or Prolonged Hospitalization

The following hospitalizations are not considered SAEs in this clinical trial:

- Admissions per protocol for a planned medical/surgical procedure. Planned hospital admissions or planned surgical procedures for an illness or disease that existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs, unless they occur at a time other than the planned date for a reason such as a worsening of the underlying disease/illness/symptoms.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.

Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

9.2.4.9. Pregnancy Exposure and Birth Events Reporting

Andexanet is not expected to have reproductive or developmental toxicity based on the following:

- Andexanet is intended for single-dose administration and, therefore, has limited potential for reproductive or developmental toxicity.
- Andexanet is a biotechnology-derived protein that is a modification of an endogenous protein in the coagulation cascade (FXa).
- Andexanet has a very short $t_{½}$ (1–2 hour effective $t_{½}$).
- Andexanet was designed as a universal antidote for FXa inhibitors, which are prescribed primarily in elderly patient populations that are not of reproductive capacity.

However, it is recommended that women of childbearing potential must use highly effective methods of contraception through at least 1 month following study drug dose. Additionally, men with sexual partners of childbearing potential must use highly effective methods of contraception for the entire duration of the study and for at least 1 month following study drug and must refrain from attempting to father a child or donating sperm in the month following the administration of study drug. The definition of highly effective methods of contraception follow the Clinical Trial Facilitation Group recommendations [31].

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a female study patient becomes pregnant or a female partner of a male study patient suspects she is pregnant, the Investigator should be informed immediately. The Sponsor must, in turn, also be notified by the Investigator immediately by completing a Pregnancy Form. If a female partner of a male study patient is pregnant or suspects she is pregnant, the male patient will be advised by the study Investigator to have his pregnant partner inform her treating physician immediately. The pregnancy must be followed up through delivery or other fetal outcome and information reported on a Pregnancy Follow-up form. For any abnormal fetal outcome (including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth), the Investigator should promptly report the abnormal fetal outcome to the Sponsor on an SAE form.

10.0 STUDY ASSESSMENTS

Assessments, testing, and treatment schedules are detailed in Appendix A. No reference to timing or frequency is described below.

10.1. Baseline Assessments

10.1.1. Informed Consent

An IRB/EC approved informed consent will be administered prior to performing study specific procedures or assessments. Administering informed consent is a process and will be documented in source documents. The current IRB/EC version of the consent will be used. See Section 13.2 for additional details on informed consent procedures.

10.1.2. Demographics

Demographics will record the age, sex, race, and ethnicity of patients. Race will be recorded (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific, White), and ethnicity will be recorded as Hispanic or Latino or Non-Hispanic or Latino.

10.1.3. Medical History

Patients will have a detailed medical history completed as part of baseline assessments. Diagnosis, year of onset and status will be reported. Status will consist of an end date or documentation as ongoing for the condition. Diagnosis should be documented and not signs and symptoms. Events with current treatment will have the treatment recorded in concomitant medications and therapies.

10.1.4. Prior and Concomitant Medications

Patients will be asked about their current physician prescribed medications, over the counter medications and any herbal or nutritional supplements. The generic name is preferred for Electronic Data Capture (EDC) entry. The dose, posology, frequency, start and stop dates and the diagnosis for use will be recorded.

10.1.5. Anticoagulant Dose or Plasma Level

Patients will be asked about the brand, dose and time of last dose of their anticoagulant. For patients who received the last dose of FXa inhibitor more than 15 hours (or an unknown time) prior to start of surgery, a local anti-fXa activity level may be obtained to allow enrollment of patients with >100 ng/mL levels. See Section 10.2.1 below on details for this local testing.

10.1.6. American Society of Anesthesiologists Physical Status Classification (ASA PS)

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

10.1.7. Eligibility Assessment

Following completion of assessments and screening testing, the investigator will determine eligibility of the patient by comparing results to inclusion and exclusion criteria. Note: It is the Sponsor's policy not to grant exceptions or waivers for inclusion and exclusion criteria.

10.1.8. Patient Identification Numbers

Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have signed informed consent and met the inclusion and exclusion criteria.

10.2. Central Laboratory Testing

Samples will be taken for analysis at central laboratories to assess biomarkers informing on both safety and efficacy and include samples for the assessment of the following: anti-fXa and anti-IIa activity, TG, TFPI and immunogenicity. Specific guidance for the collection, processing, and storage of specimens for each biomarker will be described in the Laboratory Manual provided to each site. The site initiation visit will include training on the collection, processing, and storage of the samples.

Samples for analysis at central laboratories will be processed (generally to plasma) and stored frozen until shipment to a central location for distribution to the specific laboratory that conducts each type of analysis. Samples will be analyzed only for the biomarker described in the ICF and herein. Samples will be maintained in accordance with all regulatory guidance. At the end of the study conduct and completion of the clinical study report (CSR), samples will be maintained for re-analysis at regulatory request for as long as the biologic viability of the sample has been demonstrated. Once regulatory authorities have had the opportunity to review the CSR and the Sponsor believes that there are unlikely to be questions regarding the specific samples, they will be destroyed in accordance with Good Laboratory Practice guidance and appropriate regulations.

10.2.1. Anti-fXa Activity

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

Local laboratory anti-fXa activity testing may be utilized additionally by sites to ascertain eligibility (> 100 ng/ml) if the time of last dose of FXa inhibitor is greater than 15 hours (or unknown). Local laboratory testing post-andexanet administration should be done with caution due to potential invalidity of local lab results from excessive sample dilution.

10.2.2. Thrombin Generation

Thrombin generation will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Thrombin generation will be measured using a tissue factor (TF)-initiated TG assay. This assay will be performed at a Central Laboratory. Five parameters related to TG are measured: endogenous thrombin potential (ETP), peak height, time to peak height, lag time and velocity index. Endogenous thrombin potential is prospectively identified as the primary measure for TG.

10.2.3. Tissue Factor Pathway Inhibitor

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

10.2.4. Anti-IIa Activity

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

10.2.5. Antibody Testing

Determination of the possible presence of antibodies to FX (human) and FXa (human) will be done at specific time points (see Appendix A) using the modified Bethesda assay. Antibodies against andexanet and HCPs will be assessed using standard immunogenicity assays.

For any sample that is positive for antibodies against andexanet, the potential for nAb activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a Central Laboratory.

10.3. Safety Assessments (other than Adverse Events)

10.3.1. Vital Signs

Vital signs include temperature (˚C), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), and respiratory rate (respirations per minute).

10.3.2. Physical Examination

A physical examination will be performed on all patients at various time points before and after the surgical procedure. The examination will include, at a minimum, any component relevant to the indication for surgery (e.g., abdominal examination for appendicitis, hip examination for hip fracture, neurologic examination for spinal cord compression) and an assessment of the surgical incision site (post-operative only).

10.3.3. Weight

Patient weight will be recorded in kg according to the schedule of assessments in Appendix A.

10.3.4. Clinical Laboratory Testing

Blood specimens for routine chemistry and hematology will be obtained at selected time points (see Appendix A).

The following assays will be performed at the Local Laboratory:

- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, WBC differential.
- Coagulation: prothrombin time reported as the INR.
- Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin.
- Serum or urine pregnancy test (in women of child bearing potential; see Appendix D).

10.3.5. Optional Local Laboratory Testing of Anti-fXa Levels

Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion criteria. Further details and guidance on the conduct of local laboratory anti-fXa assays can be found in the Laboratory Manual for ANNEXA-S. Investigators are discouraged from evaluating anti-fXa activity with local assays after the administration of andexanet, due to the known inaccuracy of post-andexanet results caused by the large sample dilutions associated with unmodified commercial anti-fXa assays; however, if such testing is deemed necessary, it is strongly recommended that the procedures outlined in the Laboratory Manual be followed.

10.4. Intraoperative and Hospitalization Assessments

10.4.1. Surgical Intervention

All patients entering the trial are required to have an urgent need for surgical intervention. Institutional or procedural consents should be administered for the surgical intervention in accordance with local requirements and in addition to the study specific informed consent.

- The start of surgery is the initial incision.
- The end of surgery is final skin closure. If skin closure is not completed by intention, an equivalent milestone such as dressing or packing the surgical incision may be considered the end of the procedure.

10.4.2. Intraoperative Blood Loss

Investigators will report predicted blood loss and observed blood loss during surgery for each patient. Predicted blood loss must be determined by the investigator prior to the first incision. Observed blood loss will be reported as an estimate of blood loss in milliliters at the end of surgery. It is an intraoperative assessment and will not be updated for post-closure blood loss. Observed blood loss will be measured against predicted blood loss.

10.4.3. Assessment of Intraoperative Hemostasis

Intraoperative hemostasis will be captured as an investigator assessment. Categories for assessment are provide in Table 3 (Section 11.5.1).

10.4.4. Blood Products and Hemostatic Treatments

Blood products and hemostatic treatments employed as treatment prior to, during and postoperatively will be recorded. The product (generic), dose, route of administration, date and time of use will be recorded along with the reason for use.

10.4.5. Bleeding-related Diagnostic and Therapeutic Procedures

Any diagnostic and/or therapeutic procedures employed prior to, during and postoperatively will be recorded. For diagnostic procedures, the procedure, date, time, results and relevant units or description of results will be captured. Therapeutic procedures will be captured and concomitant medications/treatments with date, time, and posology (if applicable).

As a concomitant treatment, Investigators will record the product (generic name), date, time, indication, and posology of colloid or crystalloid treatments used to support hemodynamic status.

10.4.6. Record Hours in Hospital Care Units

Investigators will record the date and time of entry into each care unit of the hospital. The date and time of entry and exit for each unit will be reported. This will be locally variable, but categories should be reconciled to the standards below:

- Emergency Department (ED): a unit dedicated to medical and surgical patients in need of immediate care.
- Intensive Care/Critical Care Department (ICU): a specialty medical unit for patients that are seriously ill are maintained under constant medical observation.
- Operating Room (OR): the room where the surgical procedure actually takes place.
- Post-anesthesia Care Unit (PACU): a specialty unit for providing post-anesthesia care for patients recovering from anesthesia.
- General Hospital Department or General Surgical Department: Covers a wide range of types of surgery and procedures on patients.

10.5. End of Study Assessments

Patients will have their survival status reported by phone on the Day 30 or End of Study visit. This assessment will record the patient's status as alive or provide the date, time, and cause of death. Note: see Section 9.0 for AEs reported for all deaths.

11.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study objectives and study design are described in Sections 2.0 and 3.1, respectively. The information in this section is a summary of the planned statistical analyses. Further details will be provided in the Statistical Analysis Plan.

11.1. General Considerations

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

Unless otherwise specified, all confidence intervals (CIs) will be 2-sided and reported at the 95% confidence level.

11.2. Randomization

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

11.3. Analysis Populations

11.3.1. Enrolled Population

The enrolled population will consist of all patients enrolled (signed informed consent and met inclusion/exclusion criteria) into the study irrespective of whether they received andexanet or not.

11.3.2. Safety Analysis Population

The safety analysis population will consist of all patients enrolled and treated with any amount of andexanet. All safety analyses will be based on the safety analysis population.

11.3.3. Efficacy Analysis Population

The efficacy analysis population will include all enrolled patients who receive any amount of andexanet treatment, undergo surgery, and have a baseline anti-fXa activity analyzed by central laboratory at or above the evaluability threshold (75 ng/mL for apixaban, edoxaban and rivaroxaban, and 0.25 IU/mL for enoxaparin). The primary, secondary, and exploratory efficacy endpoint will be analyzed based on the efficacy analysis population.

11.4. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized for all populations listed above. Data will be summarized using descriptive statistics of frequencies for categorical data and means, medians, standard deviations, minimums, and maximums for continuous data. No inferential analyses of these data are planned.

11.5. Efficacy Endpoints and Analyses

Analysis of primary, secondary, and exploratory efficacy endpoints will be based on the Efficacy Analysis Population.

11.5.1. Definitions

Hemostasis will be assessed from the start of surgery to the end of the procedure. Categories for the assessment of intraoperative hemostasis are provided in Table 3.

Table 3: Intraoperative Hemostasis Categories

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

* Tranexamic acid excluded.

The evaluation period for anti-fXa activity covers the period of time from 5 minutes following the end of the andexanet bolus to just prior to the end of the andexanet infusion. The baseline measurement will be the last value obtained prior to andexanet treatment.

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

11.5.2. Efficacy Endpoints

11.5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of effective hemostasis, as determined by the surgeon's assessment of intraoperative hemostasis and confirmed by adjudication by an independent EAC (see Table 3).

For each patient, hemostasis will be considered to be effective if the intraoperative hemostasis category is Excellent or Good, and ineffective if the intraoperative hemostasis category is Moderate or Poor.

A patient will be deemed non-evaluable if s/he meets the criteria specified in the EAC Charter.

11.5.2.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion.

Patients who do not have at least 1 anti-fXa activity level within the evaluation period will have percent decrease imputed as 0.0% (i.e., using the baseline value as the nadir value).

11.5.2.3. Exploratory Efficacy Endpoints

The following efficacy endpoints will be analyzed as exploratory:

- Relationship between intraoperative hemostasis and anti-fXa activity.
- Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, number of patients with percent reduction from baseline > 80%.
- Reversal of anticoagulant effect as measured by TG parameters (with ETP as the primary measure).
- Occurrence of receiving 1 or more RBC transfusions from start of the andexanet bolus through 12 hours after the end of surgery.
- The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the end of surgery.
- The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery.
- Observed amount of intraoperative blood loss.
- Difference between observed blood loss and predicted blood loss.
- Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery.
- Time from the signing of informed consent to the start of surgery.
- Time from clinical presentation at treatment facility to the start of surgery.
- Length of index hospitalization, assessed at the Day 30 visit.
- Time hospitalized in a PACU, assessed at the Day 30 visit.
- Time hospitalized in an ICU, assessed at the Day 30 visit.
- Length of surgery.
- Total time in OR.
- Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post enrollment).

- Occurrence of post-surgical major bleeding, as defined by ISTH criteria (see Section 4.1), within 12 hours after the end of the initial surgery.
- Occurrence of re-operations for bleeding, including for surgical wound hematomas, within 12 hours after the end of the initial surgery.
- Change from baseline in TFPI activity post-administration of andexanet.
- Change from baseline in anti-IIa activity (only patients taking enoxaparin).

11.5.3. Statistical Methodology for Endpoint Analyses

All efficacy analyses will be performed on the efficacy analysis population.

The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI.

The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median.

For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.

11.6. Determination of Sample Size

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

11.7. Safety Endpoints and Summaries

Safety will be assessed by examining the following endpoints and analyzed in the Safety Analysis Population:

- AEs (including SAEs), vital signs, physical examinations, and clinical laboratory measurements.
- TEs within 30 days of enrollment, including those suspected and confirmed by adjudication.
- Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality.
- Antibodies to FX, FXa, andexanet, and HCPs.

11.7.1. Adverse Events

Treatment-emergent adverse events, including preferred terms defined by the Medical Dictionary for Regulatory Activities (MedDRA), will be summarized by system organ class. Arterial and venous thromboembolic events, considered AESIs, will be summarized separately.

The number of events, the number of patients, and the percentage of patients who experienced at least 1 TEAE will be presented. The TEAEs that are considered by the Investigator to be related to the andexanet, TEAEs that lead to early withdrawals, and serious TEAEs will be summarized in the same manner. Frequent TEAEs will also be summarized.

All potential post-surgical bleeding events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event. Postoperative major bleeding events will be additionally adjudicated by the EAC.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

11.7.2. Thrombotic Events

All TEs will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event.

11.7.3. Deaths

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

11.7.4. Laboratory Parameters

Clinical laboratory parameters performed at the Central Laboratory (e.g., anti-fXa activity and TG) will be summarized by time point. For patients with anti-fXa activity levels obtained by a local laboratory assay for purposes of eligibility (for patients with a time from last dose greater than 15 hours), values will be documented but not formally analyzed.

Baseline values, the values at each subsequent visit, and changes from baseline will be summarized for each of the quantitative laboratory assessments.

11.7.5. Vital Signs

Vital signs will be summarized using actual values and change from baseline at pre-specified time points for each treatment group. Descriptive statistics, including threshold-based outlier analyses, will be presented.

11.7.6. Physical Examinations

Findings on physical examination will be summarized in a listing.

11.7.7. Antibodies

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

11.8. Interim Analyses

No interim efficacy analyses are planned for this Phase 2 study. During the conduct of the study, interim monitoring of safety data by the DSMB will commence after 50 patients are enrolled, then performed periodically at a frequency of approximately every 6 months.

11.9. Subgroup Analyses

Consistency of efficacy across important subgroups will be investigated within each cohort. At a minimum, primary efficacy will be summarized for subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, baseline anti-fXa activity categories (e.g., above and below thresholds of 30 ng/mL, 50 ng/mL, 75 ng/mL), procedure type (e.g., orthopedic, abdominal, thoracic, neurosurgical), duration of surgery (≤ 2 hours, 2-4 hours, > 4 hours), and volume of blood loss (above and below the median). Other subgroup analysis may be considered based on the actual enrollment. Further detail of the subgroup analysis will be described in the Statistical Analysis Plan.

12.0 STUDY COMMITTEES AND COMMUNICATIONS

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

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

13.0 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1. Institutional Review Board or Independent Ethics Committee

The protocol and ICF for this study must be reviewed and approved by an appropriate IRB or IEC before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, ICH, GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by the Sponsor Pharmaceuticals, Inc. before initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or IEC, and to the Sponsor.

13.2. Informed Consent

Each patient must be provided with oral and written information describing the nature and duration of the study, and the patient must sign a written ICF in a language in which he/she is fluent before study-specific procedures are conducted. The signed and dated ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF. Due to the critical nature of the illness under study and the possibility that patients will be unable to provide their own consent, proxy consents (defined as consent from a legally authorized representative) are allowed if permissible by national regulatory authorities or local/regional laws and regulations. Emergency consent is not permitted.

13.3. Documentation

The Investigator must provide the Sponsor with the following documents (copies of which must be maintained by the Investigator):

1. Curriculum vitae of the Investigator and any sub-investigators listed on the Form FDA 1572.
2. A signed copy of the IRB or IEC approval notice for protocol and informed consent.
3. A copy of the IRB- or IEC-approved ICF.
4. Laboratory certification with a list of normal values for laboratory tests that will be conducted at local laboratories.
5. Completed financial disclosure form for the Investigator and any sub-investigators listed on the Form FDA 1572.

13.4. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant EDC system, as appropriate. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Some clinical laboratory data will be collected externally from the EDC systems. Further details for data collection and data handling will be specified in the data management plan, eCRFs, instructions for completing forms, other data handling procedures, and procedures for data monitoring. The MedDRA coding dictionary will be used for coding AEs, medical history conditions, and procedures. The reconciliation of the SAEs between the clinical and safety databases will be conducted as specified in plans determined and approved prior to study start-up. The WHO-DD dictionary will be used to code medications.

13.5. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.6. Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Sponsor's Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate eCRF. Deviations due to non-compliance that render subject non-evaluable for key endpoints will be considered significant deviations. Any other changes in the protocol will be made as an amendment to the protocol and must be approved by the Sponsor and the IRB or IEC — before the changes or deviations are implemented. The Sponsor will not assume any

responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol.

13.7. Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the US FDA and the study sponsor and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential. Conduct of this study will comply with the EU's General Data Protection Regulation.

13.8. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates andexanet was received from the Sponsor and prepared for the study, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies can be destroyed at the site if available, in accordance with approved written procedures, or returned to the Sponsor after written authorization is obtained from the Sponsor's Clinical Development. In addition, no onsite destruction or drug returns will be performed without having accountability and verification of study drug performed first. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 13.5.

13.9. Study Monitoring

The Investigator will allow representatives of the Sponsor to periodically review (at mutually convenient times before, during, and after the study has been completed) all eCRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents, including documents that support patients' eligibility (e.g., medical history, concomitant medications) should be made available to the study monitor. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

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15.0 LIST OF APPENDICES

Appendix A: Schedule of Activities

Appendix B: Disseminated Intravascular Coagulation (DIC) Scoring Algorithm [33]

Appendix C: Definitions of Cardiogenic Shock, Sepsis and Septic Shock [34]

Appendix D: Definition of Female of Childbearing Potential

Appendix E: Guidance for Submission of Potential Thrombotic Events for Adjudication

Appendix F: American Society of Anesthesiologists Physical Status Classification

APPENDIX A. SCHEDULE OF ACTIVITIES

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

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

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

ADX = andexanet; AE = Adverse event; ASA = American Society of Anesthesiologists; BP = Blood pressure; CBC = Complete blood count; ED = Emergency department; EoII = End of Initial Infusion; EoS = End of Surgery; ET = Early Termination; FX = Factor X; FXa = Activated factor X; h = Hour(s); HCP = Host-cell protein; HR = Heart rate; ICU = Intensive care unit; INR = International normalized ratio; min = Minute(s); nAb = Neutralizing antibody (activity); OR = operating room; PACU = Post-anesthesia care unit; PT = Prothrombin time; RR = Respiratory rate; SoS = Start of Surgery; TE = thrombotic event; Temp = Temperature; TFPI = Tissue factor pathway inhibitor

[1] The EoS time point may occur before the EoII; EoS procedures should be carried out when EoS occurs.

[2] Collect EoS samples within 15 minutes from the end of surgery but before stopping infusion.

[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.

[4] Approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

[5] Prior to the first incision, predicted blood loss must be determined by the investigator.

[6] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.
[7] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.

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

APPENDIX B. DISSEMINATED INTRAVASCULAR COAGULATION (DIC) SCORING ALGORITHM [33]

Note: Algorithm should only be used for patients with an underlying disorder known to be associated with overt DIC. A score of ≥ 5 is compatible with overt DIC.

Laboratory Test	Result	Score
Platelet Count	≥ 100 x 10^9 / L	0
	< 100 x 10^9 / L	1
	< 50 x 10^9 / L	2
D-Dimer, Fibrin Degradation Products	No increase	0
	Moderate increase	2
	Strong increase	3
Prothrombin Time	< 3 seconds	0
	≥ 3 but < 6 seconds	1
	≥ 6 seconds	2
Fibrinogen Level	≥ 1 g/L	0
	< 1 g/L	1

APPENDIX C. DEFINITIONS OF CARDIOGENIC SHOCK, SEPSIS AND SEPTIC SHOCK [34]

Cardiogenic shock is a cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion [35]. The definition of cardiogenic shock may be clinically determined and consists of the following: Systolic blood pressure (SBP) < 90 mmHg for at least 30 minutes, OR

- Hemodynamic support required to maintain SBP ≥ 90 mmHg, AND
- End-organ hypoperfusion (e.g., urine output < 30 mL/hr or cool extremities)

Cardiogenic shock may also be optionally defined by hemodynamic criteria obtained through invasive hemodynamic monitoring:

- Cardiac index ≤ 2.2 L/min/m^2, AND
- Pulmonary capillary wedge pressure ≥ 15 mmHg

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [36]. Organ dysfunction can be identified as an acute change in total Sequential [sepsis-related] Organ Failure Assessment (SOFA) score ≥ 2 points consequent to the infection (Table 4) [37].

- The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
- A SOFA score ≥ 2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with the Quick SOFA (qSOFA) criteria, i.e., alteration in mental status, systolic blood pressure ≤ 100 mmHg, or respiratory rate ≥ 22/min [36].

Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.

- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥ 65 mmHg and having a serum lactate level > 2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Table A4: SOFA Scoring System

Component	Score
PaO_2/FiO_2 (mmHg)	
≥ 400	0
≥ 300 and < 400	+1
≥ 200 and < 300	+2
≥ 100 and < 200 AND mechanically ventilated	+3
< 100 AND mechanically ventilated	+4
Glasgow Coma Scale	
15	0
13-14	+1
10-12	+2
6-9	+3
< 6	+4
Hemodynamic Criteria	
Mean arterial pressure ≥ 70 mmHg	0
Mean arterial pressure < 70 mmHg	+1
Dopamine dose ≤ 5 μg/kg/min OR dobutamine (any dose)	+2
Dopamine > 5 μg/kg/min OR epinephrine ≤ 0.1 μg/kg/min OR norepinephrine ≤ 0.1 μg/kg/min	+3
Dopamine > 15 μg/kg/min OR epinephrine > 0.1 μg/kg/min OR norephinephrine > 0.1 μg/kg/min	+4

APPENDIX D. DEFINITION OF FEMALE OF CHILDBEARING POTENTIAL

All women of childbearing potential (including those who have had a tubal ligation) will have a urine or serum pregnancy test at screening. If the pregnancy test is positive, andexanet should not be administered.

All female patients are considered to be of childbearing potential unless they meet 1 of the following criteria:

1. The patient has been post-menopausal (amenorrheic) for at least 1 year.
2. The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to screening.
3. The patient had a hysterectomy.

APPENDIX E. GUIDANCE FOR SUBMISSION OF POTENTIAL THROMBOTIC EVENTS FOR ADJUDICATION

Adjudication criteria for the diagnosis transient ischemic attacks, strokes, myocardial infarctions (MIs), venous thromboembolism, and arterial systemic embolism are provided below.

Transient Ischemic Attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with signs or symptoms lasting < 24 hours and no evidence of new infarct on neuroimaging if performed. Investigators should consider submitting cases for adjudication if an event meets this definition.

Stroke is defined as an acute episode of neurological dysfunction consistent with a vascular cause. A stroke will be considered to have occurred if there is a rapid onset of signs and/or symptoms of a new persistent neurological deficit consistent with an obstruction to cerebral blood flow with no apparent nonischemic cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours or, for symptom onset less than 24 hours, have neuroimaging evidence of new infarct. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. For the diagnosis of stroke, the following criteria must be fulfilled:

- Rapid onset of a focal/global neurologic deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body, dysphagia/aphasia, hemianopia, amaurosis fugax, or other new neurological signs/symptoms consistent with stroke.
- The duration of a focal/global neurologic deficit is at least 24 hours, OR the neurological deficit results in death, OR there is neuroimaging evidence of a new infarct.
- There is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion).
- Confirmation of the diagnosis by at least 1 of the following: specialist evaluation, or brain imaging procedure (i.e., computed tomography [CT] scan, magnetic resonance imaging [MRI] scan, cerebral vessel angiography).

If the acute neurological signs represent a worsening of a previous (baseline) deficit, the new signs must have either persisted for more than 1 week, or persisted for more than 24 hours and were accompanied by an appropriate new imaging finding.

Investigators should consider submitting cases for adjudication as a possible stroke if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., delirium, mental status changes) that are not otherwise explainable by an alternative etiology.

Since the adjudication of hemostatic efficacy encompasses changes in clinical neurologic function and hematoma volume, these findings will only be considered for thrombotic event adjudication if they clearly have an ischemic etiology.

Myocardial Infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis of MI:

- Detection of a risk and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the upper limit of normal (ULN) and with at least 1 of the following:
  - Symptoms of ischemia.
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block.
  - Development of pathological Q waves in the electrocardiogram (ECG).
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block (LBBB), but death occurred before biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (> 5 × ULN) in patients with normal baseline values or a rise of cTn values> 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic ECG changes, (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the ULN.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 × ULN) in patients with normal baseline cTn values. In addition, either (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Investigators should consider submitting cases for adjudication as a possible MI if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., angina, ventricular tachyarrhythmia, cardiogenic shock, heart failure) that are not otherwise explainable by an alternative etiology.

Venous Thromboembolism is defined as a symptomatic deep vein thrombosis (DVT) or PE confirmed by objective testing. Criteria for the objective confirmation of DVT include:

- A constant filling defect in 2 or more views on contrast venography in 1 or more proximal venous segments (iliac, common femoral, superficial femoral, popliteal).
- New or previously undocumented non-compressibility of 1 or more venous segments on compression ultrasound.
- A clearly defined intraluminal filling defect on contrast enhanced CT.

Criteria for the objective confirmation of PE include:

- An intraluminal filling defect on pulmonary angiography.
- Sudden contrast cut-off of 1 or more vessels more than 2.5 mm in diameter on a pulmonary angiogram.
- A high probability ventilation-perfusion (VQ) scan (1 or more segmental perfusion defects with corresponding normal ventilation).
- An abnormal non-high VQ scan plus criteria for the diagnosis of DVT.
- An unequivocal, intra-arterial, un-enhancing filling defect in the central pulmonary vasculature (pulmonary trunk, main pulmonary arteries, anterior trunk, right and left interlobar and lobar arteries) on CT.

Investigators should consider submitting cases for adjudication as a possible VTE if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., lower extremity swelling, respiratory failure) that are not otherwise explainable by an alternate etiology. All cases of unexplained sudden death should also be submitted for adjudication as a possible PE and/or MI.

Arterial systemic embolism is defined as abrupt vascular insufficiency associated with clinical and other objective evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs and symptoms must be consistent with embolic arterial occlusion, and there must be clear evidence of abrupt occlusion of a systemic artery, with at least 1 type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report. Investigators should consider submitting potential systemic arterial embolism cases for adjudication if they meet this definition.

APPENDIX F. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION

ASA PS 1	Normal healthy patient
ASA PS 2	Patients with mild systemic disease
ASA PS 3	Patients with severe systemic disease
ASA PS 4	Patients with severe systemic disease that is a constant threat to life
ASA PS 5	Moribund patients who are not expected to survive without the operation
ASA PS 6	A declared brain-dead patient whose organs are being removed for donor purposes

ASA = American Society of Anesthesiology; PS = Physical Status

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO REQUIRE URGENT SURGERY (ANNEXA-S)

DRUG NAME:	Andexanet alfa (PRT064445)
PROTOCOL NUMBER:	19-515
PHASE:	3
TRIAL SPONSOR:	Portola Pharmaceuticals, Inc. PPD South San Francisco, CA 94080
MEDICAL MONITOR:	PPD, MD Medical Director Clinical Development Portola Pharmaceuticals, Inc. Phone: PPD Fax: PPD email: PPD
PROTOCOL DATE:	Original: 16 September 2019 Amendment 1: 19 November 2019

Confidentiality Statement

This protocol is the property of Portola Pharmaceuticals, Inc. It is a confidential communication. Acceptance implies an agreement not to disclose information contained herein that is not otherwise publicly available, with the exception that it may be disclosed to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the purpose of obtaining approval to conduct the study. The IRB/IEC is requested and expected to maintain confidentiality. This document may not be used or published without the consent of Portola Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Portola Pharmaceuticals, Inc.

Signature of Principal Investigator

Name of Principal Investigator (Print) Date (DD Month YYYY)

SPONSOR'S AGREEMENT

I have read the attached protocol entitled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

PPD

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Medical PPD tor
Clinical Development
Portola Pharmaceuticals, Inc.

20112019
Date (DD Month YYYY)

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LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
andexanet alfa	Recombinant factor Xa inhibitor antidote, PRT064445
ASA	American Society of Anesthesiologists
AUC	Area under the curve
CABG	Coronary artery bypass grafting
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum observed concentration
CT	Computed tomography
cTn	Cardiac troponin
D-dimer	Fibrin degradation product
DIC	Disseminated intravascular coagulation
DOAC	Direct oral anticoagulant
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ERCP	Endoscopic retrograde cholangio-pancreatography
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
ETP	Endogenous thrombin potential
F1+2	Prothrombin fragment 1 and 2
FDA	(United States) Food and Drug Administration
FFP	Fresh frozen plasma
FIO_2	Fraction of inspired oxygen
FX	Factor X
FXa	Factor Xa (activated factor X)
GCP	Good Clinical Practice

Term	Definition
HCP	Host-cell protein
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous
LBBB	Left bundle branch block
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
min	Minute
MRI	Magnetic resonance imaging
nAb	Neutralizing antibody (activity)
OR	Operating room
PACU	Post-anesthesia care unit
PaO_2	Partial pressure oxygen-arterial
PCC	Prothrombin complex concentrate
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PRBC	Packed red blood cell
PS	Physical status
PT	Prothrombin time
RBC	Red blood cell
rfVIIa	Recombinant factor VIIa
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure

Term	Definition
ST-T	ST-segment T wave
t½	Terminal half-life
TAT	Thrombin-antithrombin
TE	Thrombotic event
TEAE	Treatment-Emergent Adverse Event
Temp	Temperature
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TG	Thrombin generation
TIA	Transient ischemic attack
TXA	Tranexamic acid
ULN	Upper limit of normal
US	United States
VKA	Vitamin K antagonist
VQ	Ventilation-perfusion
VTE	Venous thromboembolism
WBC	White blood cells
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study Title	Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)
Study Number	19-515
Study Phase	3
Number of Sites	Approximately 120 sites Globally
Objectives	In patients requiring urgent surgery who are being treated with a direct or indirect Factor Xa (FXa) inhibitor, the objectives of this study are as follows: **Primary Objective:** • To evaluate hemostatic efficacy following andexanet alfa (andexanet) treatment. **Secondary Efficacy Objective:** • To evaluate the effect of andexanet on anti-fXa activity. **Exploratory Efficacy Objectives:** • To evaluate the effect of andexanet on thrombin generation (TG). • To evaluate the use of red blood cell (RBC) transfusions. • To evaluate the use of non-RBC, non-platelet blood products and hemostatic agents. • To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir. • To evaluate the time from obtaining informed consent (study consent) to the start of surgery. • To evaluate the length of index hospitalization, intensive care unit (ICU) stay, time in a post-anesthesia care unit (PACU), time in the operating room (OR), and length of surgery. • To evaluate the occurrence of re-hospitalization. • To evaluate the occurrence of post-surgical major bleeding. • To evaluate the occurrence of re-operations for bleeding. • To evaluate the effect of andexanet on tissue factor pathway inhibitor (TFPI) activity. • In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity. **Safety Objective:** • To evaluate the overall safety of andexanet.
Efficacy Endpoints	**Primary Efficacy Endpoint:** • The achievement of hemostatic efficacy as determined by the surgeon's assessment of intraoperative hemostasis and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC). **Secondary Efficacy Endpoint:** • The percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion.

	Exploratory Endpoints: • Relationship between hemostatic efficacy and anti-fXa activity. • Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, number of patients with percent reduction from baseline > 80%. • Reversal of anticoagulant effect as measured by TG parameters (with endogenous thrombin potential as the primary measure). • Occurrence of receiving 1 or more RBC transfusions from the start of the andexanet bolus through 12 hours after the end of surgery. • The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the end of surgery. • The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery. • Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery. • Length of time from the signing of informed consent to the start of surgery. • Length of time from clinical presentation at the treating facility to the start of surgery. • Length of index hospitalization, assessed at the Day 30 visit. • Time hospitalized in a PACU, assessed at the Day 30 visit. • Time hospitalized in an ICU, assessed at the Day 30 visit. • Length of surgery. • Time in the OR. • Occurrence of re-hospitalization, within 30 days of enrollment, including number of days and length of re-hospitalization (through 30 days post enrollment). • Occurrence of post-surgical major bleeding, as defined by International Society on Thrombosis and Haemostasis (ISTH) criteria, within 12 hours after the start of the initial surgery. • Occurrence of re-operations for bleeding, including surgical wound hematomas, within 12 hours after the end of the initial surgery. • Change from baseline in TFPI activity post-administration of andexanet. • Change from baseline in anti-IIa activity (only patients taking enoxaparin).
Safety Measurements	• Adverse events (AEs) (including serious AEs [SAEs]), vital signs, physical examinations, and clinical laboratory measurements. • Thrombotic events (TEs) within 30 days of enrollment, including suspected and confirmed by adjudication. • Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality. • Antibodies to FX, FXa, andexanet, and host-cell proteins (HCPs).
Study Design	This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery, and who have, within 15 hours prior to surgery, received their last dose of 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. If the time from last dose is unknown, or greater than 15 hours prior to surgery, the patient may be enrolled provided a local laboratory anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin). In such cases the start of

Study Design (cont'd)	surgery must begin no greater than 4 hours after the blood collection for the local anti-fXa activity test. The prespecified time periods and anti-fXa activity level thresholds are designed to ensure patients have sufficiently high anti-fXa activity levels. The Efficacy Analysis Population for the study will only include patients whose central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin). The start of surgery must be within 15 hours following the last dose of FXa inhibitor. Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an intravenous (IV) bolus administered over 15 to 30 minutes (depending on dose) immediately prior to the start of surgery (skin incision). The bolus must be completely administered before the start of surgery (i.e., at the first incision; designated Time 0). The bolus must be immediately followed by an IV infusion that will continue for a minimum of 2 hours, irrespective of the duration of the surgery. The infusion should continue from start to end of surgery (skin incision to skin closure). The treating surgeon will assess hemostatic efficacy at the conclusion of the procedure (i.e., skin closure). Additional andexanet, be it for extended infusion or re-dosing, may be given at the discretion of the Investigator when specific criteria are met (see "Test Product, Dose, and Mode of Administration" below). The independent EAC will adjudicate all deaths, TEs, post-surgical bleeding events (e.g., surgical hematomas), and hemostatic efficacy. The independent EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter. All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. In addition, patients who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit.

Study Periods	The study duration for any individual patient will be up to 37 days. There are 4 study periods. Study periods are defined as follows:
	• Screening Period: Day 1.
	• Pre-surgical Assessment Period: Day 1.
	• Treatment Period: Day 1.
	  o Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~2.5 hours) but no greater than a total 6.5 hours (including both the initial regimen and the extended infusion).
	  o Re-dosing (low dose bolus and infusion) may occur within 12 hours after completion of the first course of andexanet treatment (but after the conclusion of the surgical procedure) if protocol specified criteria are met, at the investigators discretion.
	• Safety Follow-up Period: Days 1–30 + 7.

Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or their medical proxy (or legal designee) has given written informed consent. 2. Age ≥ 18 and < 85 years old. 3. Requires urgent surgical intervention that must occur within 12 hours of consent, for which reversal of anti-fXa activity is judged necessary. 4. Received 1 of the following FXa inhibitors apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d) within 15 hours prior to start of surgery. If the time from the last dose is unknown or greater than 15 hours, the patient may be

	enrolled provided a local laboratory anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin). 5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential). 6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).
Exclusion Criteria	If a patient meets any of the following criteria, he or she is not eligible: 1. Surgery for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low. 2. Acute life-threatening bleeding (ISTH criteria) at the time of Screening: a. The patient has acute-overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained. b. The patient has overt bleeding associated with a fall in hemoglobin level by ≥2g/dL, OR, a hemoglobin ≤8 g/dL if no baseline hemoglobin is available. c. The patient has acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal. 3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the intraoperative use of systemic, intravascular, unfractionated heparin. 4. Primary procedure for efficacy assessment is a non-surgical interventional procedure (e.g, lumbar puncture, skin biopsy, cardiac catheterization, endoscopic retrograde cholangio-pancreatography). 5. Expected survival of < 1 month due to comorbidity. 6. Known "Do Not Resuscitate" order or similar advanced directive. 7. The patient has a recent history (within 30 days prior to screening) of a diagnosed TE as follows: venous thromboembolism (including deep vein thrombosis, pulmonary embolism, intracardiac thrombus), myocardial infarction (including asymptomatic troponin elevations), disseminated intravascular coagulation, acute traumatic coagulopathy, cerebrovascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease. 8. Acute decompensated heart failure or cardiogenic shock at the time of screening. 9. The patient has severe sepsis or septic or severe hemorrhagic shock at the time of Screening. 10. The patient has heparin-induced thrombocytopenia (with or without thrombosis). 11. Inherited coagulopathy (e.g., anti-phospholipid antibody syndrome, protein C/S deficiency, Factor V Leiden) 12. Last dose of apixaban < 2.5 mg, rivaroxaban < 10 mg, edoxaban < 30 mg, or enoxaparin 40 mg. 13. The patient is pregnant or a lactating female. 14. The patient has received any of the following drugs or blood products within 7 days of enrollment: o Vitamin K antagonists (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (e.g., NovoSeven®). o Whole blood, plasma fractions. Note: Administration of tranexamic acid, platelets or packed red blood cells is not an exclusion criterion. 15. The patient was treated with an investigational drug < 30 days prior to Screening. 16. Prior treatment with andexanet.

Test Product, Dose, and Mode of Administration

The andexanet IV bolus will be initiated within 30 minutes prior to the start of surgery (i.e., the first incision) and must be completed prior to surgery start. The bolus will be followed by a continuous infusion lasting at least 120 minutes, irrespective of the length of the surgery. The continuous infusion must be ongoing at the start of surgery, and must continue until the end of surgery even if extended treatment is required. There are 2 possible dosing regimens as described below:

Andexanet Dose	Timing of Last Dose of FXa Inhibitor	Initial Dose		Extended Infusion
		Initial IV Bolus	Initial Follow-on IV Infusion	
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban 10 mg • Apixaban 5 mg • Enoxaparin 40 mg • Edoxaban 30 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery	Extended infusion (beyond 120 minutes) may be administered at **4 mg/min** (low-dose) for up to 4 additional hours*
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **> 15 hours or unknown time** • Local anti-fXa > 100 ng/mL (0.5 IU/mL for enoxaparin)	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery	

***Extended Infusion (Additional low-dose 4mg/min infusion up to 4 hours)**

Following the primary andexanet bolus and 120-minute infusion, the andexanet infusion will be continued at the low dose of andexanet (4 mg/min) if the surgery extends longer than the primary bolus and infusion. The extended infusion (1) must continue at least through the end of the surgery and (2) may additionally continue during the immediate post-operative period (per investigator discretion), and (3) should not exceed 4 hours.

Maximum Length of Dosing (Initial Bolus + 120 minute Infusion + Extended Infusion, < 6.5 hours):

The total duration of dosing including initial bolus, 120-minute infusion, and any extended infusion, should not exceed 6.5 hours. The limit of planned duration of infusion is stipulated to balance declining anti-fXa plasma levels and acceptable exposure to andexanet.

	Criteria for Re-Dosing with Andexanet Consider re-dosing with andexanet (**low-dose bolus + 120 min infusion**) only if: a) New, clinically significant, surgery-related post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b) The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c) Re-dosing initiation occurs within 12 hours after the completion of the surgical procedure.
Reference Therapy, Dose, and Mode of Administration	Not applicable.
Sample Size	Approximately 200 patients will be enrolled. After accounting for 10 to 25% attrition (e.g., canceled surgeries, discontinued and/or non-evaluable patients, or baseline anti-fXa activity analyzed by central laboratory less than the evaluability threshold), a sample size of 150 or 180 patients will provide an estimate of the proportion of patients achieving effective (excellent or good) hemostatic efficacy with a margin of error (half width of the 95% confidence interval) that is less than 8% or 7.3%, respectively. Additionally, with 150 to 180 patients, there will be 78% to 84% chance to observe a rare event with 1% occurrence rate.
Statistical Analysis Methods for Efficacy	All efficacy analyses will be performed in the Efficacy Analysis Population. All hypothesis tests and confidence intervals (CI) will be 2-sided with α=0.05. The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI. The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.
Statistical Analysis Methods for Safety	All safety analyses will be performed in the Safety Analysis Population. Safety will be assessed by examination of 30-day survival status, AEs (including SAEs and TEs), vital signs, physical examination, centrally adjudicated deaths, clinical laboratory measurements, and antibodies to andexanet, FX, FXa, and HCPs. These data will be descriptively summarized. All potential post-surgical major bleeding events and TEs will be confirmed by adjudication.

1.0 INTRODUCTION

1.1. Background

The class of oral anticoagulants known as direct Factor Xa (FXa) inhibitors (Direct Oral Anticoagulants [DOACs]) has consistently demonstrated comparable or superior efficacy and/or safety relative to its predecessors, Vitamin K Antagonists (VKAs) and Low Molecular Weight Heparins. These agents (apixaban [Eliquis®], betrixaban [BevyxXa®], edoxaban [Savaysa®], rivaroxaban [Xarelto®]) are approved for the prevention of serious thromboembolic outcomes (e.g., stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], venous thromboembolism [VTE] in hip or knee replacement surgery) and have become widely used in the United States (US) and globally. One limitation to the use of FXa inhibitors has been the lack of an antidote to be used in cases of severe and/or life-threatening bleeding events or urgent or emergency surgery. In the case of the latter, it has been estimated, based on analyses from pivotal studies of oral anticoagulants, that approximately 1% of anticoagulated patients may require urgent surgery within 2 years of initiation [1, 2]. As the use of DOAC agents increase, the need to reverse anticoagulation related to this class of drugs is expected to increase.

Andexanet, a rationally designed, recombinant analog of endogenous human FXa, has been developed to rapidly and potently reverse FXa inhibition and restore physiologic coagulation. Data from Phase 2, Phase 3, and ongoing Phase 3b/4 studies have shown that andexanet rapidly reverses FXa inhibition in healthy volunteers and in bleeding patients [3]. Andexanet is also associated with a high rate of clinical hemostasis in patients with acute major bleeding [4]. Importantly, however, andexanet has not been evaluated in patients requiring urgent surgery. The present trial will be performed to demonstrate improved hemostatic efficacy with andexanet in patients requiring urgent surgery receiving an oral FXa inhibitor.

Andexanet was granted accelerated approval by the US Food and Drug Administration (FDA) on 03 May 2018 and was granted conditional marketing authorization by the European Commission on 26 April 2019, for the treatment of patients with life-threatening bleeding while taking apixaban and rivaroxaban. The confirmatory randomized controlled trial in patients with intracranial hemorrhage, ANNEXA-I, is currently ongoing. Andexanet is not currently indicated for FXa reversal in patients requiring urgent surgery.

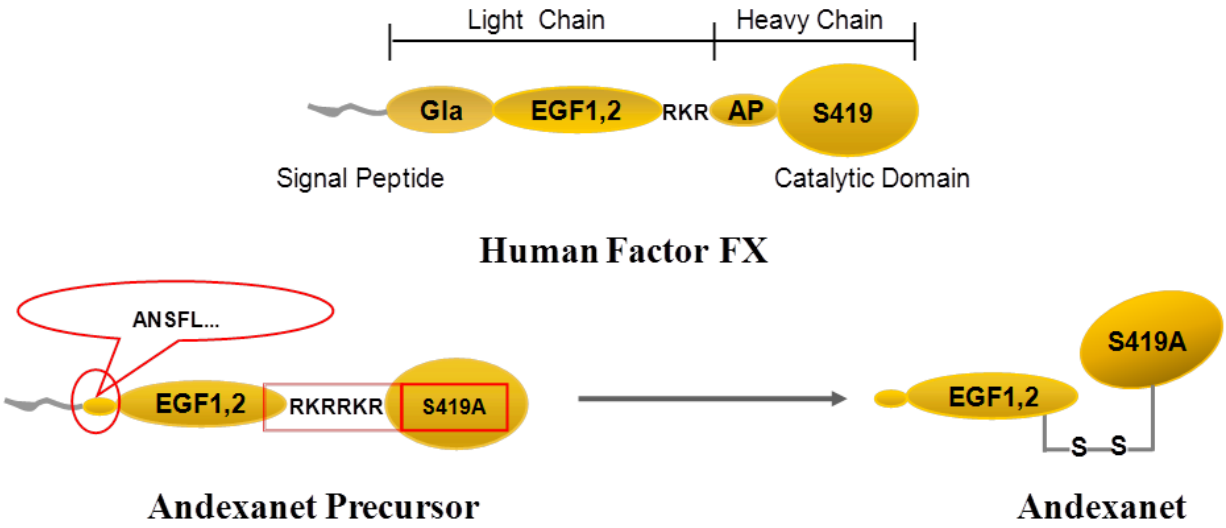
1.2. Description of Andexanet

Andexanet is a recombinant version of human FXa that has been modified to render it functionally inactive (Figure 1). To achieve this aim, 2 key structural modifications were made to native human FXa. First, the substitution of a serine residue with an alanine at the active site eliminated the protein's catalytic activity. Second, the removal of the Gla domain eliminated the ability to assemble into a prothrombinase complex, thereby removing potential intrinsic anticoagulant effects. Reversal of anticoagulation is achieved because andexanet retains the

ability to bind FXa inhibitors with high affinity, thereby sequestering them and preventing them from binding to and inhibiting native FXa.

Additional information about the mechanism and structure of andexanet can be found in the Investigator's Brochure.

Figure 1: Structures of Human Factor X and Andexanet



1.3. Summary of Relevant Nonclinical Experience with Andexanet

Nonclinical studies in several species (mice, rats, rabbits, pigs, and cynomolgus monkeys) have demonstrated that the anticoagulant effects of direct and indirect FXa inhibitors were reversed by andexanet, resulting in a return to normal hemostasis.

Functional studies with the direct FXa inhibitors have been undertaken to explore the effectiveness of andexanet to reverse injury-induced bleeding in anticoagulated animals using the well-characterized rodent tail transection models and a modified rabbit liver laceration model. In these studies, andexanet was administered either prior to (prophylactic model) or following (treatment model) organ injury to mimic the clinical settings of urgent (emergent) surgery or massive bleeding as a result of trauma. In both the prophylactic and treatment models, significant reductions in blood loss were observed in andexanet-treated animals vs vehicle controls. The decrease in blood loss following andexanet administration correlated with a decrease in pharmacodynamics (PD) markers of anticoagulation, including anti-fXa activity, international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time, depending on the inhibitor and species. Collectively, in these models, andexanet dose-dependently reduced the anticoagulant effects of the direct FXa inhibitors, requiring a minimum molar ratio of ~1:1, andexanet:direct FXa inhibitor for maximal inhibition of anti-fXa activity.

Andexanet has also been tested in a pig polytrauma model designed to evaluate its efficacy in a setting with a greater severity of bleeding. Using German landrace pigs anticoagulated with apixaban (20 mg/day for 4 days), the effect of an intravenous (IV) bolus (1,000 mg) of andexanet versus a bolus (1,000 mg) plus a 2-hour infusion (10 mg/min) was studied when andexanet was administered after crush injury to a single lobe of the liver, followed by bilateral femur fracture. Following andexanet treatment (12 minutes after injury) with a bolus alone, there was a rapid drop in anti-fXa levels to near zero, which returned to placebo levels ~2 hours later. With bolus plus infusion, the anti-fXa levels remained low throughout the duration of the infusion and then gradually returned to placebo levels approximately 2 hours after the end of infusion. With regard to bleeding, anticoagulation with apixaban resulted in an approximately 2-fold increase in blood loss 12 minutes after injury. In the control group (administered placebo), there was a subsequent increase in blood loss over time to 3,403 ± 766 mL, and 100% of the animals exsanguinated with a mean survival time of 135 minutes (range 92–193 minutes). Treatment with andexanet resulted in a significant reduction in total blood loss post-injury: 57% (1,264 ± 205 mL) and 59% (1,202 ± 94 mL) for bolus alone and bolus plus infusion of andexanet, respectively. All andexanet-treated animals survived for the duration of the observation period (5 hours).

The toxicology of andexanet was evaluated in both rats and monkeys. Because the intent was to administer andexanet to reverse the anticoagulant effect of FXa inhibitors and thereby restore baseline hemostasis, studies in monkeys were conducted with andexanet administered alone as well as co-administered with FXa inhibitors. Andexanet was well-tolerated in both species at all dose levels. The highest dose administered in both species was 60 mg/kg/day (single day [only in monkeys] and 2-week repeat dose studies) and was the No Observed Adverse Effect Level. In monkeys the 60 mg/kg/day dose resulted in exposure levels 2-3-fold above those observed in clinical studies at the high therapeutic dose.

1.4. Summary of Relevant Clinical Experience with Andexanet

Andexanet has been studied in approximately 545 healthy subjects thus far in Phase 1 to 3 studies, as well as in 352 patients presenting with an acute major bleeding event while receiving an FXa inhibitor in the ongoing Phase 3b/4 (ANNEXA-4) study. In addition, andexanet was administered to a single preoperative patient taking apixaban who required emergency surgery to treat necrotizing fasciitis [5]. Finally, there are 5 other ongoing studies; 4 in healthy volunteers: a Phase 2 study to investigate the reversal of the pharmacologic effects of the oral FXa inhibitor, betrixaban; a Phase 2 study to evaluate the pharmacokinetics (PK), PD, safety, and tolerability of andexanet in individuals of Japanese descent; and 2 Phase 1 studies to compare the PK of andexanet produced by 2 manufacturing processes; and 1 study in patients: a randomized controlled clinical trial to evaluate the clinical efficacy and safety of andexanet in patients with intracranial hemorrhage while taking direct FXa inhibitors.

Completed trials include a single ascending dose Phase 1 study (Study 11-501) in 32 healthy subjects; a Phase 1 study (Study 14-506) examining the PK and PD of andexanet in 10 young vs. 10 older subjects receiving apixaban; a Phase 1 PK/PD study (Study 16-512) to evaluate the PK, PD, safety, and tolerability of andexanet produced by an updated manufacturing process (Generation 2); a Phase 2 dose-ranging study (Study 12-502) in 157 healthy subjects to determine the appropriate doses to reverse the anticoagulant effects of apixaban, rivaroxaban, enoxaparin and edoxaban; and 2 Phase 3 studies in 148 healthy older subjects (50-75 years) to confirm that the doses defined in the Phase 2 study reverse apixaban (Study 14-503) or rivaroxaban (Study 14-504). Details of the completed studies may be found in the Investigator's Brochure.

1.4.1. Phase 1 Study of Andexanet Alone in Healthy Subjects (11-501)

Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, tolerability, PK, and PD of andexanet in 32 healthy subjects, each of whom received 1 of 4 doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.6.

1.4.2. Phase 1 Study of Andexanet in Healthy Younger Versus Older Subjects (14-506)

Study 14-506 was a Phase 1 randomized, open-label study of andexanet in healthy younger (18-45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban for 3 hours and then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin generation (TG) in older and younger subjects were similar. The safety data from this study are summarized in Section 1.4.6.

1.4.3. Phase 1 PK/PD Study to Evaluate the PK, PD, Safety, and Tolerability of Andexanet Produced by an Updated Manufacturing Process (Generation 2) (16-512-Direct Inhibitors)

Study 16-512-Direct Inhibitors was a randomized, double-blind, placebo-controlled study in healthy volunteers dosed to steady state with FXa inhibitors, designed to: 1) demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes; 2) evaluate the degree to which Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo; and 3) evaluate the safety and tolerability of Generation 2 andexanet. A total of 122 subjects were enrolled in the study. Generation 1 and Generation 2 andexanet were found to have PK comparability when administered at low doses, though strict bioequivalence criteria were not met with high dose andexanet. That said, Generation 1 and Generation 2 andexanet were observed to be comparable for the primary PD parameter of anti-fXa activity at both low and high doses of andexanet. The safety data from this study are summarized in Section 1.4.6.

1.4.4. Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects (12-502)

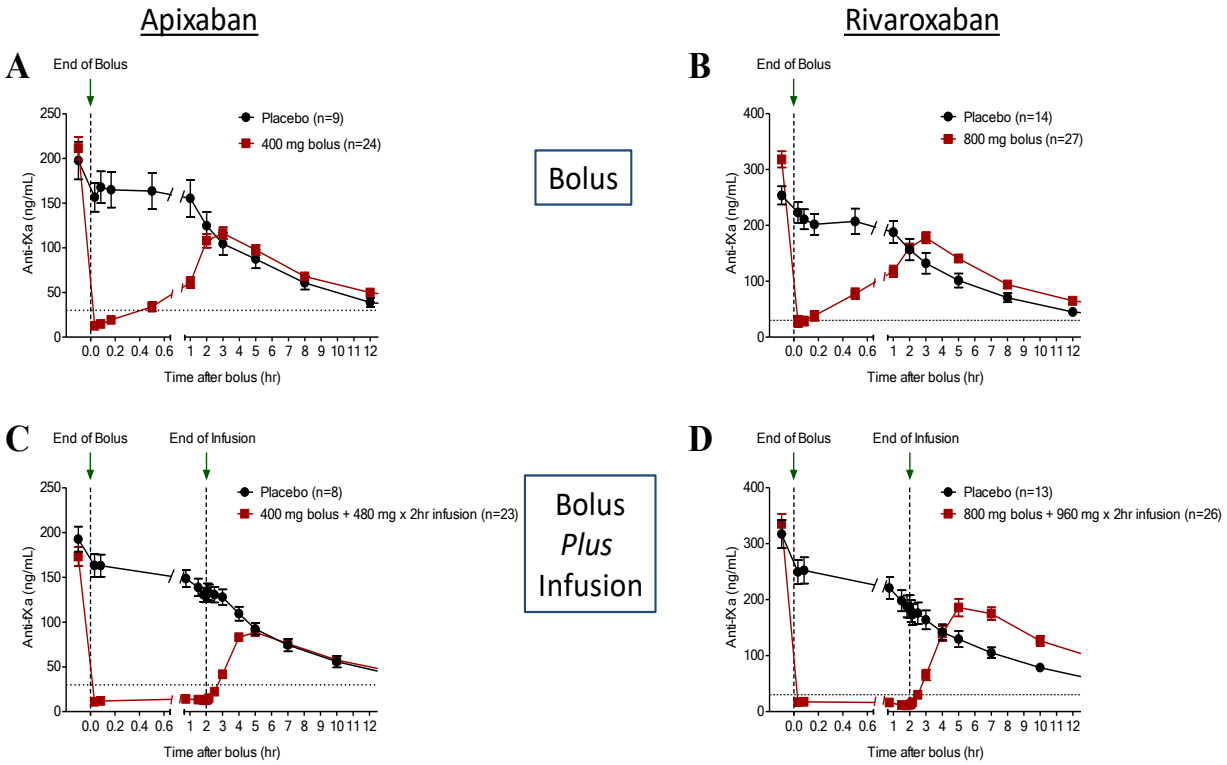
The dose-finding Study 12-502 was a Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in healthy subjects receiving 1 of 4 direct or indirect FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Each FXa inhibitor was examined in a separate study module, within which multiple dosing regimens of andexanet were given in cohorts of 9 healthy subjects (6 active, 3 placebo). The anticoagulant was dosed to steady state over 5 to 6 days, before administration of andexanet or placebo on Study Day 6. Depending on the anticoagulant dose, the total dose of andexanet across dosing cohorts ranged from 90 to 1,760 mg. Healthy subjects were then followed through Study Day 13 in a domiciled Phase 1 study unit and, subsequently, through Day 48 as outpatients.

Andexanet exhibited dose-proportional PK for both maximum observed concentration (C_{max}) and area under the curve (AUC) with a mean terminal half-life ($t_{½}$) of approximately 4 hours. Administration of andexanet also resulted in a dose-dependent reduction in anti-fXa activity for each of the FXa inhibitors. Additionally, the downstream anticoagulant effects of apixaban, rivaroxaban, and edoxaban were reversed in a dose-dependent fashion by administration of andexanet, as evaluated by the measurement of TG. These effects were consistent with restoration of hemostatic mechanisms after andexanet administration. The safety data from this study are summarized in Section 1.4.6.

1.4.5. Phase 3 Studies in Healthy Older Volunteers (14-503 and 14-504)

Two randomized, double-blind, placebo-controlled studies were designed to evaluate reversal of anticoagulation in older subjects (ages 50-75 years) anticoagulated with apixaban (Study 14-503) or rivaroxaban (Study 14-504). In these studies, the anticoagulant was dosed to steady state over 4 days (rivaroxaban) or 3.5 days (apixaban) before administration of andexanet or placebo on Study Day 4. The subjects were then followed through Study Day 8 in a domiciled Phase 1 study unit and, subsequently, through Day 43 as outpatients. Andexanet was administered either as an IV bolus (Part 1) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). Reversal of anticoagulation was measured using anti-fXa activity, anticoagulant free fraction, TG, and other coagulation markers. A single IV bolus of andexanet significantly reversed the anti-fXa activity of apixaban and rivaroxaban, reduced unbound apixaban and rivaroxaban concentrations, and restored normal TG (Figure 2), with the maximal effect observed within 2 minutes of the end of the bolus administration. The safety data from this study are summarized in Section 1.4.6.

Figure 2: Rapid Onset and Significant Reduction of Apixaban and Rivaroxaban Anti-fXa Activity in Older Healthy Subjects by Andexanet (Study 14-503 and Study 14-504)



fXa = activated factor X; hr = hour; IV = intravenous

Legend: Anti-fXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion.

A. Apixaban – with andexanet 400 mg IV bolus

B. Rivaroxaban – with andexanet 800 mg IV bolus

C. Apixaban – with andexanet 400 mg IV bolus plus 4 mg/minute infusion for 120 minutes

D. Rivaroxaban – with andexanet 800 mg IV bolus plus 8 mg/minute infusion for 120 minutes

Note: A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-fXa activity following andexanet treatment. The points on the graph represent the mean anti-fXa activity level and error bars illustrate standard error. There was a statistically significant difference ($P < 0.05$) in the percent change of anti-fXa activity normalized to pre-bolus between andexanet and placebo until 2 hours after administration of bolus (Part 1) or infusion (Part 2). The horizontal dashed-line represents the anti-fXa activity at 30 ng/mL, the estimated non-effective level for FXa inhibition [6].

1.4.6. Summary of Safety from Clinical Studies of Healthy Subjects

Andexanet has been generally well tolerated in healthy volunteers in the Phase 1, 2, and 3 studies at single doses up to 1,760 mg, with no apparent pattern of safety signals with the exception of mild-moderate infusion reactions. A single adverse event (AE) (bilateral pneumonia) met serious adverse event (SAE) criteria in the Phase 1 study 11-501. This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred approximately 3 weeks after

dosing. No severe or life-threatening AEs have been reported. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent, and have rarely required treatment (2 subjects received 1 dose each of diphenhydramine). With the exception of 2 subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting.

Andexanet was associated with dose-dependent increases in prothrombin fragment 1 and 2 (F1+2), thrombin-antithrombin (TAT), and fibrin degradation product (D-dimer), and with a concomitant decrease in tissue factor pathway inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with clinical evidence of thrombosis. Compared with administration of andexanet alone (Study 11-501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of an anticoagulant.

In all completed studies to date, among healthy subjects treated with andexanet, approximately 11% developed low-titer non-neutralizing antibody (nAb) to andexanet. There have been a small number of very low-titer non-nAbs to FX and FXa, with the titer value for all positive samples occurring at the minimum required dilution. However, there have been no nAbs to FX or FXa.

1.4.7. Phase 3b/4 Study in Patients with Acute Major Bleeding (14-505)

Study 14-505 (ANNEXA-4) is an ongoing, multi-national, prospective, open-label, single-arm clinical study of andexanet in patients with acute major bleeding while taking an FXa inhibitor (specifically apixaban, edoxaban, enoxaparin, or rivaroxaban). As of 01 June 2018, 352 patients had been enrolled in the study. Baseline characteristics included a mean age of 77 years, 47% female, 87% Caucasian, and median body mass index 27 kg/m^2. A total of 90 patients (26%) had gastrointestinal bleeding, 227 patients (64%) had an intracranial hemorrhage, and 35 patients (10%) had other types of bleeding.

Of the 352 enrolled patients, 254 were considered efficacy evaluable, defined as having a major bleed confirmed by adjudication, and a baseline anti-fXa activity of 75 ng/mL or greater (≥ 0.25 IU/mL for enoxaparin patients). In efficacy-evaluable patients taking apixaban and rivaroxaban, the median reduction from baseline in anti-fXa activity was > 90%. Overall, of 249 patients with evaluable hemostatic efficacy, 204 (81.9%) had excellent or good hemostatic efficacy. Of these, 171 (68.7%) were adjudicated as having excellent hemostatic efficacy and 33 (13.3%) as having good hemostatic efficacy. Of the efficacy evaluable patients presenting with intracranial hemorrhage, the rate of excellent or good hemostatic efficacy was 80.4%.

Of the 352 patients in the Safety Population, 250 patients (71.0%) experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs (occurring in ≥ 5% of patients) by preferred term were urinary tract infection in 31 patients (8.8%) and pneumonia in 21 patients (6.0%). A total of 32 patients (9.1%) experienced AEs that were considered by the Investigator to be possibly or probably related to andexanet. The most frequent treatment-related events were pyrexia (4 patients; 1.1%), ischemic stroke (4 patients; 1.1%), and headache and nausea (3 patients each; 0.9%).

Serious adverse events were experienced by 144 patients (40.9%). The most common SAEs (occurring in ≥ 2% of patients) were pneumonia in 11 patients (3.1%) and respiratory failure in 9 patients (2.6%). Seventeen (4.8%) patients experienced at least 1 treatment-related SAE. The most frequently reported SAEs that were considered by the Investigator to be possibly or probably related to andexanet were ischemic stroke (3 patients; 0.9%), and DVT, myocardial infarction (MI), cerebral infarction, cerebrovascular accident, and PE (2 patients each; 0.6%).

There have been 54 deaths (15.3%) prior to the Day 30 visit; of these, 37 were adjudicated as cardiovascular deaths and 12 as non-cardiovascular deaths. Overall, the mortality rate was consistent with the expected burden of AEs in this patient population given the vascular risk factors, overall high morbidity, and poor prognosis of patients with acute major bleeding.

A total of 34 patients (9.7%) with any bleeding type experienced an adjudicated clinical thrombotic event (TE). While re-anticoagulation rates were similar between patients with and without TEs, the time to resumption of anticoagulation was markedly greater in patients with TEs.

No clinically meaningful changes in laboratory values related to andexanet (including hematocrit and hemoglobin) were detected in the study. Similarly, no clinically significant changes in vital signs and/or physical examination findings have been observed. Twenty patients (5.7%) had confirmed positive results for anti-andexanet antibodies after treatment. The titers were nearly all low values with no neutralizing activity in any patient samples.

A randomized clinical trial (Study 18-513, ANNEXA-I) is currently underway to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage.

2.0 STUDY OBJECTIVES

In patients requiring urgent surgery who are being treated with a direct or indirect FXa inhibitor, the objectives of this study are described in the subsections that follow.

2.1. Primary Objectives

- To evaluate the hemostatic efficacy following andexanet treatment.

2.2. Secondary Efficacy Objectives

- To evaluate the effect of andexanet on anti-fXa activity.

2.3. Exploratory Efficacy Objectives

- To evaluate the effect of andexanet on TG.
- To evaluate the use of red blood cell (RBC) transfusions.
- To evaluate the use of non-RBC, non-platelet blood products, and hemostatic agents.
- To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir.
- To evaluate the time from obtaining informed consent (study consent) to the start of surgery.
- To evaluate the length of index hospitalization, intensive care unit (ICU) stay, time in a post-anesthesia care unit (PACU), time in the operating room (OR), and length of surgery.
- To evaluate the occurrence of re-hospitalization.
- To evaluate the occurrence of major post-surgical bleeding, including surgical wound hematomas.
- To evaluate the occurrence of re-operations for bleeding.
- To evaluate the effect of andexanet on TFPI.
- In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity.

2.4. Safety Objectives

- To evaluate the overall safety of andexanet, including AEs, SAEs, vital signs, physical examinations, clinical laboratory measurements, thrombotic events (TEs), mortality, and immunogenicity.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery (must occur within 12 hours of consent) who have, within 15 hours prior to surgery, received 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. The start of surgery must be within 15 hours following the last dose of FXa inhibitor. If the time from last dose of FXa inhibitor is unknown or greater than 15 hours, patients with a local anti-fXa activity level obtained within 2 hours prior to consent > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin) may be enrolled. In such cases the start of surgery must begin no greater than 4 hours after the blood collection for the local test. The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have sufficiently high anti-fXa activity levels.

Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an IV bolus of andexanet administered over approximately 15 to 30 minutes (depending on dose), followed immediately by an IV continuous infusion of andexanet for 2 hours, irrespective of the duration of surgery. The bolus must be completed immediately prior to the start of surgery (i.e., at the first incision; designated as Time 0). The infusion should continue from prior to the start of surgery (initial skin incision) until the end of surgery (close of skin incision). If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes). Additional andexanet, be it for extended treatment or re-dosing, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or postoperative complications are met (see Section 6.2).

The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the surgeon's assessment of intraoperative hemostasis using a pre-specified 4-point scale (Section 11.5.1) and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC).

In addition to hemostatic efficacy, the EAC will adjudicate all deaths, TEs, and post-surgical major bleeding events (e.g., surgical hematomas). The EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter.

All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. The study schedule of activities can be found in Appendix A.

3.2. Blinding and Randomization

3.2.1. Randomization

There is no randomization in this study. All eligible patients will be enrolled and receive open-label andexanet treatment.

3.2.2. Blinding

This study will be open-label. However, the EAC will be blinded to all anti-fXa levels.

3.3. Duration of Study

The duration of the study for any individual patient will be up to 37 days.

There are 4 study periods. Study periods in the study for the respective cohorts are defined as follows:

- Screening Period: Day 1.
- Pre-surgical Assessment Period: Day 1.
- Treatment Period: Day 1.
  - Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~ 2.5 hours) but no greater than a total of 6 hours (including both the initial regimen and the extended infusion).
  - Re-dosing (low dose bolus and infusion) may occur within 12 hours after completion of the first course of andexanet treatment if protocol specified criteria are met, at the investigators discretion. [refer to Section 6.2]).
- Safety Follow-up Period: Days 1–30 + 7.

3.4. Discussion of Study Design, Including Choice of Control

3.4.1. Study Population

The study will enroll patients between the ages of 18 and 85 years who have recently taken an FXa inhibitor within 15 hours prior to start of surgery and who require urgent surgery for which reversal of anti-fXa activity is judged necessary.

If the time from last dose is unknown or greater than 15 hours, the patient may be enrolled provided a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin]). In such cases the start of surgery must be no greater than 4 hours after the blood collection time for the local test.

Patients who are in need of urgent surgery within 12 hours of consent may be enrolled. Patients undergoing procedures for which the risk of clinically meaningful uncontrolled or unmanageable

bleeding is low are not eligible. Patients with life-threatening bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition, see Section 4.2) are also not eligible.

It is expected that eligible procedures may have varying degrees of tissue trauma but still have clinically relevant bleeding risk for which the reversal of FXa inhibition is judged necessary. For example, surgeries in a confined space (e.g., spinal cord decompression) can be considered to be at high bleeding risk even with relatively little tissue trauma, as opposed to an intra-abdominal surgery. Anticipated surgery types may include, but are not limited to, abdominal, thoracic, orthopedic, gynecological open and laparoscopic surgery. To ensure an adequate number of patients with certain key surgery types, abdominal surgeries (including both open and laparoscopic) and orthopedic surgeries will each comprise approximately 20% of the enrolled population. Patients undergoing only non-surgical invasive procedures (e.g. skin biopsies, lumbar puncture, cardiac catheterization, ERCP) will be excluded.

To align with previous studies of andexanet [4], the Efficacy Analysis Population for the study will only include patients whose central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin).

3.4.2. Rationale for the Dose Regimen

All patients will receive 1 of 2 doses of andexanet based on the specific anticoagulant taken and timing of the last dose.

The andexanet dosing regimens to be examined in this study are as follows:

- Low dose: 400 mg IV bolus at a rate of 30 mg/min (duration of approximately 15 minutes) followed by a continuous infusion at a target rate of 4 mg/min for 120 minutes irrespective of the duration of surgery
- High dose: 800 mg IV bolus at a rate of 30 mg/min (duration of approximately 30 minutes) followed by a continuous infusion at a target rate of 8 mg/min for 120 minutes irrespective of the duration of surgery

Extended infusion at the low-dose (4 mg/min) may be administered for up to an additional 4 hours after initial dosing (bolus + infusion) is completed (1) in order to ensure mandatory continuous infusion from start to end of surgery, and (2) may continue into the immediate post-operative coverage per investigator discretion. Total dosing time (initial bolus + 120 minute infusion + any extended infusion) should be less than 6.5 hours.

Evidence to support this dosing regimen comes from PK/PD modeling that included results from the ANNEXA-4 study in bleeding patients. Data from the Phase 3 studies with apixaban and rivaroxaban, as well as a recently completed Phase 1 study of Generation 2 andexanet in healthy volunteers (Study 16-512-Direct Inhibitors; Section 1.4.3), confirm the levels of FXa inhibition and recovery of TG observed in the Phase 2 study. These doses of andexanet correspond to

decreases in anti-fXa activity that correlate with normalization of hemostasis as measured by a TG assay. The change to the lower dose (400 mg) at 8 hours after the last administered FXa inhibitor dose was based on the PK-PD model that predicted the time at which equivalent anti-fXa activity reversal and TG normalization would be achieved.

In addition to the above, the doses for this study (19-515) were shown to substantially reduce anti-fXa activity and increase TG in a Phase 3b/4 study in which andexanet was given to patients receiving an FXa inhibitor who had acute major bleeding (ANNEXA-4).

3.4.3. Rationale for Extended Infusion or Re-Dosing of Andexanet

In this study, there is potential for patients to require additional andexanet treatment beyond what is initially stipulated (bolus + 120-minute infusion). For example, unpredictable events during surgery may prolong the duration of surgery. Based on clinical judgement of procedural or patient factors, the treating physician may determine that the infusion should additionally extend to the immediate postoperative period. In addition, a surgical patient may bleed after completion of surgery. Therefore, extended andexanet infusions (to address longer surgeries) and re-dosing of andexanet (for post-surgical bleeding events) will be implemented in the protocol.

A low-dose continuous infusion (4 mg/min) for up to an additional 4 hours was selected as the regimen to use for extended infusions, whereas a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes) will be used for re-dosing. The rationale for these dosing levels is based on the premise that the amount of reversal agent required to neutralize an FXa inhibitor diminishes as the inhibitor is eliminated over time.

Investigators will be required to document in the electronic case report form (eCRF) the clinical justification for why subjects require extended infusion of andexanet or additional dosing of andexanet during surgery. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for extended duration of dosing or re-dosing during surgery are outlined in Section 6.2.

Re-dosing Criteria:

Factors that may determine if re-dosing is appropriate include the treating surgeon's consideration of patient factors, such as degree of visible bleeding, hemodynamic stability, need for hemostatic support products, or to avoid reoperation to control bleeding. The Investigator may also consider clinical suspicion that the patient has levels of FXa inhibition sufficient to contribute to bleeding based on patient factors such as time from last FXa inhibitor dose, safety assessments required by the protocol or routine care and renal function. Additionally, the need for re-operation to control bleeding may be considered reason re-dose to avoid the additional procedure.

3.5. Safety Plan and Monitoring

The study will be conducted in patients who are hospitalized. As such, treatment with andexanet and subsequent monitoring will be done in a medical setting. It is expected that patients requiring urgent surgery will remain hospitalized for at least 12 hours, the timeframe for the primary efficacy evaluations. During the first 12-hour period (Study Day 1), AEs, vital signs, physical examinations, and laboratory testing will be performed as indicated in Appendix A to monitor safety. Survival status will be ascertained on Study Day 30, and, if applicable, cause of death will be recorded. Antibody samples will be taken at baseline and Day 30 to assess immunogenicity against andexanet, FX, FXa, nAb, and HCPs.

Of the 352 patients, 9.7% of patients with acute major bleeding in ANNEXA-4 experienced protocol-defined, adjudicated TEs that occurred within 30 days of andexanet treatment. While the attributability of these events to andexanet is uncertain, it is significantly possible that they will occur in the current study, given the anticipated enrolled population, for which reversal of anticoagulation may expose the underlying risk of TEs, and andexanet's known effects on coagulation biomarkers such as D-dimer, F1+2, and TFPI. In this study, patients with TEs within 30 days of Screening, those with a history of hypercoagulable states, and those who received procoagulant products within 7 days of Screening will not be eligible for the study due to their much greater risk for TEs in general and following anticoagulation reversal. In this study, TEs will be considered AEs of special interest (AESIs) and will be reported within 24 hours to the Sponsor. Thrombotic events, both suspected and confirmed by adjudication, will be tracked as safety endpoints for the study. To mitigate the risk of TEs, Investigators are encouraged to consider resumption of an anti-thrombotic agent (preferably oral) as soon as it is clinically appropriate. Additional clinical precautions to mitigate thrombotic risk in postoperative care such as early mobilization, sequential compression devices or other routine measures should also be strongly considered.

Prior and ongoing clinical studies have identified infusion reactions of mild or moderate intensity as an AE related to administration of andexanet (described in Section 1.4.5). Patients in this study will receive andexanet in an inpatient, monitored setting under medical supervision and immediate access to resuscitative measures. Infusion reactions observed in prior and ongoing studies have had their onset during the infusion itself.

Whether or not patients have been discharged from the hospital, they will undergo the Study Day 2, Study Day 3, and Follow-up Day 30 visits to assess safety. Due to the theoretical possibility of antibody formation to andexanet, FX, FXa, or HCPs, antibody testing will be performed at baseline and at the Study Day 30 visit.

The independent EAC, in addition to adjudicating the primary endpoint, will also adjudicate all TEs, deaths, and all post-surgical bleeding events using pre-defined criteria as described in their charter. A DSMB will review all safety data on a schedule described in the DSMB charter. In

addition, safety data will be reviewed by the Sponsor at an ongoing basis. Guidelines for the management of specific AEs are provided in Section 8.0.

3.6. Benefit and Risk Assessment

Factor Xa inhibitors are a significant therapeutic advance in several indications. However, a significant risk of anticoagulation with FXa inhibitors is the potential for uncontrolled bleeding. In the case of urgent surgery, a delay in surgical treatment necessary to sufficiently diminish anti-coagulant concentrations could potentially result in deleterious clinical consequences. While andexanet is approved for the management of acute major bleeding related to FXa inhibitor use, it is unknown whether it is efficacious and safe in patients who require urgent surgery in the setting of recent use of an FXa inhibitor. Andexanet may be beneficial in reversing anticoagulation due to FXa inhibition and, thus, facilitating normal hemostasis during the surgical procedure. In addition to any personal benefit to individual patients, there is a potential benefit to all current and future patients treated with andexanet (and, more generally, all patients taking FXa inhibitors) from the insights gained through this clinical study.

The risks of study participation involve the risk of experiencing an AE related to andexanet or to the study procedures. To date, no major safety issues directly attributable to andexanet have definitively emerged in clinical studies. However, whenever chronic anticoagulation is reversed in patients with an indication to receive it, the risk of thromboembolic events is increased. Additionally, surgical intervention can also increase thromboembolic risk. This risk must be balanced against the potential for new or worsening bleeding related to the surgery. The PD effect of andexanet is short. Therefore, shortly after the infusion is discontinued and once the potential for bleeding is minimized, it will be possible to return the patient to a therapeutically anticoagulated state as needed. It is recommended that the Investigator carefully weigh the risk of new bleeding against the risk of thrombosis when considering when to resume anticoagulation for the patient.

Procedural risks inherent to the urgent surgical procedure itself would vary based on the procedure type and individual patient risk factors, and should be additionally communicated to the patient by the treating physician.

The safety monitoring plan for this study is robust (see Section 3.5), including treatment of patients in a hospital setting, an approximate 30-day safety follow-up, ongoing review of safety data by the Sponsor and independent safety reviews by the DSMB as well as adjudication of TEs, deaths, hemostatic efficacy, and post-surgical bleeding events by the EAC.

Based on the above considerations, the potential risks to patients in this study are justifiable. Patients or their legally authorized representative will be consented as to the potential risks and will be required to sign an informed consent form (ICF), documenting their understanding of these risks and willingness to participate in the study.

4.0 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1. Inclusion Criteria

All of the following criteria must be met for the patient to be eligible to participate in the study:

1. Either the patient or his or her medical proxy (or legal designee) has given written informed consent prior to Screening.
2. Age ≥ 18 and < 85 years old.
3. Requires urgent surgical intervention that must occur within 12 hours of consent, for which reversal of anti-fXa activity is judged necessary.
4. Received 1 of the following FXa inhibitors apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d) within 15 hours prior to start of surgery. If the time from the last dose is unknown, or greater than 15 hours and a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin), the patient may be enrolled.
5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential).
6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).

4.2. Exclusion Criteria

If a patient meets any of the following criteria, he or she is *not* eligible to participate:

1. Surgery for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low.
2. Acute life-threatening bleeding (ISTH criteria [7]) at the time of Screening:
    a. The patient has acute-overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise explained.
    b. The patient has overt bleeding associated with a fall in hemoglobin level by ≥2g/dL, OR, a hemoglobin ≤8 g/dL if no baseline hemoglobin is available.
    c. The patient has acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal.
3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the intraoperative use of systemic, intravascular, unfractionated heparin.

4. Primary procedure being considered for efficacy evaluation is a non-surgical interventional procedure (e.g, skin biopsy, lumbar puncture, cardiac catheterization, endoscopic retrograde cholangio-pancreatography).
5. Expected survival of < 1 month due to comorbidity.
6. Known "Do Not Resuscitate" order or similar advanced directive.
7. The patient has a recent history (within 30 days prior to Screening) of a diagnosed TE as follows: VTE (including DVT, PE, intracardiac thrombus); MI (including asymptomatic troponin elevations); disseminated intravascular coagulation (DIC); acute traumatic coagulopathy; cerebrovascular accident; transient ischemic attack; unstable angina pectoris hospitalization; or severe peripheral vascular disease (see Appendix B for DIC scoring algorithm).
8. Acute decompensated heart failure or cardiogenic shock at the time of screening (see Appendix C for cardiogenic shock definition)
9. The patient has severe sepsis or septic or hemorrhagic shock at the time of Screening (see definition in Appendix C).
10. The patient has heparin-induced thrombocytopenia (with or without thrombosis).
11. Inherited coagulopathy (e.g., anti-phospholipid antibody syndrome, protein C/S deficiency, Factor V Leiden).
12. Platelet count < 80,000/μL at the time of Screening.
13. Last dose of apixaban < 2.5 mg, rivaroxaban < 10 mg, edoxaban < 30 mg, enoxaparin < 40 mg.
14. The patient is pregnant or a lactating female.
15. The patient has received any of the following drugs or blood products within 7 days of enrollment:
    - Vitamin K antagonists (e.g., warfarin).
    - Dabigatran.
    - Prothrombin complex concentrate products (PCC, e.g., Kcentra®), recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®).
    - Whole blood, plasma fractions.
    - Note: Administration of tranexamic acid (TXA), platelets, or packed red blood cells (PRBCs) is not an exclusion criterion.
16. The patient was treated with an investigational drug < 30 days prior to Screening.
17. Prior treatment with andexanet.

4.3. Criteria for Discontinuation from the Study

A patient may elect to discontinue participation in the study at any time. However, all efforts must be made to follow patients for the full duration of the study and to encourage all patients to complete the Day 30 contact.

This study will be conducted in such a way as to minimize patients that withdraw consent. The following points will apply:

- Patients who discontinue study treatment or some procedures should not be discontinued from the study. Investigators must distinguish the difference between patients who discontinue study drug or procedures from those who withdraw consent and do not intend to participate further in the study follow-up visits or contacts (withdrawers).
- All Investigators must commit to minimizing the number of patients who do not complete the study.
- If patients cannot or will not return for visits, the Investigator (or their designee) should attempt to contact them by telephone or other means.

Reasons for all study withdrawals will be recorded in the eCRF.

4.4. Criteria for Discontinuation of Andexanet

Andexanet may be prematurely discontinued for a number of reasons, including:

- Any intolerable AE that cannot be ameliorated by appropriate medical intervention or that in the opinion of the Medical Monitor or Investigator would lead to undue risk if the patient were to continue on treatment.

Patients who discontinue study drug may still continue in the study. Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, in which case they should undergo an Early Termination visit (complete the same procedures as Day 30 Visit).

Reasons for all discontinuations of andexanet will be recorded in the eCRF.

4.5. Patient Replacement

Patients who discontinue prematurely will not be replaced.

4.6. Study Completion

Study completion for each patient is defined as completion of the Day 30 visit or, at a minimum, the time at which Day 30 mortality data are recorded.

In certain European Union Member States, “study completion” may also be considered the same as “end of trial.”

5.0 ENROLLMENT AND STUDY PROCEDURES

A summary of the patient visits and clinical evaluations can be found in Appendix A. Details on efficacy and safety assessments can be found in Section 10.0. Laboratory assessments, clinical assessments, and/or procedures performed per Investigator or institutional standard of care at presentation, but before signing of informed consent, may be used to fulfill protocol requirements.

5.1. Screening Period

Patients will be identified by their need for urgent surgery that cannot be delayed and time from last dose of an FXa inhibitor. Informed consent will be administered followed by assignment of a patient identification number. Eligibility will be assessed by completion of demographics, medical history, physical examination, determination of last time of anticoagulated dose or plasma level. Baseline safety assessment will be performed inclusive of vital signs and weight, collection of local clinical laboratory results. Baseline efficacy and safety labs will be collected for analysis by a central laboratory. Following execution of the informed consent, changes in patient status that meet the definition of AEs will be recorded (Section 9.0).

5.2. Visit Procedures (Days 1, 2, 3, and 30)

Day 1 Inpatient

On Day 1, patients will receive treatment with andexanet and will undergo the urgent surgery. Prior to start of dosing, patients will have the general health status assessed and categorized according to the American Society of Anesthesiologists Classification, repeat safety assessments (serial vital signs, repeat physical examination, and local labs). Study specific assessments and central laboratory samples will be collected to assess *in vitro* hemostasis.

The dose of andexanet will be selected based on anticoagulant product/brand, dose, and time of last dose of anticoagulant the patient is taking. The duration of the surgery will determine the total dose and duration of andexanet administered. Generally, it is planned for patients to complete the bolus and start the infusion immediately prior to the start of surgery and to receive andexanet infusion, including extended dosing as necessary, for the duration of their surgical procedure. During the surgery, the investigator and staff will provide assessment of hemostasis and record all supporting medications related to hemostasis support. Patients should remain hospitalized on Day 1. The patient will be scheduled for study Day 2 visit.

Day 2 and Day 3

Follow-up visits on Days 2 and 3 will be conducted as an inpatient or outpatient. Patients will receive safety assessments (vital signs, physical examination, and local laboratory testing) along with collection of samples for central laboratory analysis to assess hemostasis. Diagnostic and therapeutic products supporting hemostasis will be assessed, documented and reported. Adverse

events and concomitant medications will be recorded. The patient will be scheduled for study Day 30 visit.

Day 30

The Follow-up visit on Day 30 will be conducted as an inpatient or outpatient. Safety assessments will be performed (vital signs, physical examination, weight, and local laboratory testing) along with collection of samples for central laboratory analysis to assess immunogenicity and hemostasis. Adverse events and concomitant medications will be recorded. The investigator will assess and report duration of hospitalization by unit type (emergency, critical care units, post-op units, etc.) and document the survival status of the patient.

Procedures performed at the Day 30 visit will be also performed for all early terminating patients (Section 5.4).

5.3. Unscheduled Visit

During the study, additional clinical visits may be scheduled at the Investigator's discretion in order to care for the patient. The reason for an unscheduled visit will be recorded in the eCRF.

The following must be performed at an unscheduled visit:

- Record the reason for the unscheduled visit.
- Record AEs since last study visit.
- Record use of concomitant medication since last study visit.

Additional procedures may be performed at an unscheduled visit as deemed necessary by the Investigator. These may include any of the central or local laboratory testing done at scheduled visits, vital signs, additional evaluations for bleeding, or assessment of AEs. Record study specified procedures and data captured as unscheduled visits.

5.4. Early Termination Visit

An Early Termination visit will be conducted if the patient discontinues from the study before the Follow-up Day 30 visit. In addition to the Day 30 procedures outlined in Section 5.2, the following procedures will be performed at the ET visit:

- Record the reason for early termination.
- Record dates of use of anticoagulant(s) on the anticoagulant eCRF.
- Perform a final assessment of bleeding.

Vital signs and local laboratory assessments for complete blood count (CBC) should also be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.

6.0 DRUG SUPPLIES AND DOSING

6.1. Formulation

Andexanet alfa (PRT064445) is a lyophilized product for reconstitution for IV injection that is supplied by Portola Pharmaceuticals, Inc. It is supplied in single-use, type I glass vials with grey rubber stoppers and flip-off seals at a concentration of 200 mg/vial. The composition in each vial is listed in Table 1. Following reconstitution with Sterile Water for Injection, the concentration of the reconstituted solution is 10 mg/mL. The lyophilized product must be reconstituted using Sterile Water for Injection before use. For details on reconstituting/ preparing andexanet, please refer to the Pharmacy Manual.

Table 1: Reconstitution Volumes and Composition for Andexanet for Injection

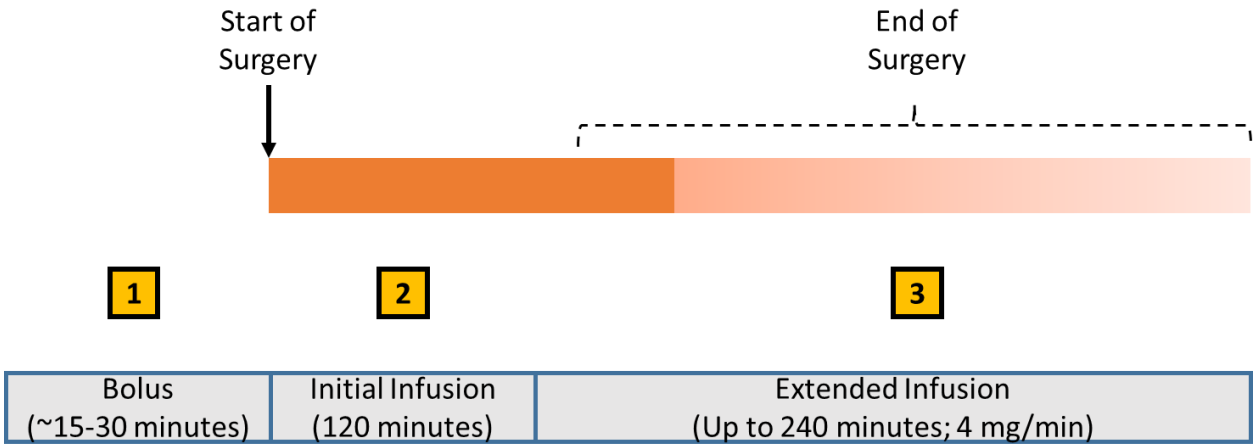
Vial Contents	**200 mg Vial**
Reconstitution Volume	**20.0 mL SWFI**
Ingredients	***Quantity per Vial***
Andexanet (PRT064445)	200 mg
Tris (Tromethamine)	6.52 mg
Tris HCl	7.33 mg
L-Arginine Hydrochloride	94.8 mg
Sucrose	200 mg
Mannitol	500 mg
Polysorbate 80	2.0 mg
Sterile Water for Injection	QS to 20 mL (removed during lyophilization process)

HCl = hydrochloride; QS = Quantity sufficient; SWFI = Sterile water for injection

6.2. Dosing and Administration

The timing of andexanet dosing in relation to the surgical procedure is depicted schematically in Figure 3.

Figure 3 Schema for Andexanet Dosing



(1) Bolus to be completed prior to start of surgery
(2) Initial infusion for at least 120 minutes, and from start to end of surgery
(3) Extended 4 mg/min infusion for up to 4 hours

Key Dosing Directives:

- Initial Bolus (low/high-dose) must be completed prior to start of surgery (initial skin incision)
- Initial dosing (low/high-dose bolus + 120-min infusion) should be completely administered irrespective of surgery length.
- Infusion should continue throughout the duration of surgery, defined as skin incision to skin closure.
- Extended infusion (up to 4 hours at 4 mg/min) (1) may be administered to ensure continuous infusion to match the duration of the surgery, and (2) can additionally proceed into the immediate postoperative period per investigator discretion.

Initial Dosing (Bolus + 2-hour infusion):

The initial andexanet dosing regimen will consist of the following:

1. an IV bolus, (to be completed prior to surgery)

   followed immediately by

2. an IV continuous infusion lasting for at least 2 hours, (irrespective of the duration of surgery).

The bolus should be initiated not more than 30 minutes before, and must be completed by, the start of surgery (i.e., at the first incision). The bolus will be followed immediately by a continuous infusion lasting at least 120 minutes, irrespective of the length of the surgery. It is

possible that the infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens (Table 2).

If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes). Note that the surgeon's assessment of intraoperative hemostasis is to occur at the end of surgery, irrespective of the total duration of andexanet infusion.

Extended Infusion (maximum of 4 additional hours at 4 mg/min)

Extended Infusion may be administered after completion of initial dose (bolus + 2-hour infusion):

1. To ensure continuous intraoperative infusion lasts the duration of the surgery**, (**if initial 2-hour infusion is completed prior to end of surgery)

   and

2. To provide coverage during the immediate postoperative period, per investigator clinical judgement

If the initial andexanet dosing regimen (bolus plus 2-hour infusion) is completed **prior** to the end of the procedure, the infusion should continue at a low dose (only 4 mg/min) at least through the end of the surgery (skin closure).

Extended infusion may also continue after the end of surgery per investigator clinical judgement if deemed appropriate for the immediate post-operative period.

To facilitate the extended infusion, approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

Allowable Total Length of Dosing (Initial + Extended = up to 6.5 hours):

The total length of the initial dosing duration of andexanet (initial infusion plus extended infusion) should last no longer than 6.5 hours. Total study drug administration greater than 6.5 hours, while not prohibited, is strongly discouraged.

Re-dosing:

If a post-operative patient meets the applicable criteria for andexanet re-dosing (Table 2), he/she may be re-dosed. All patients that are re-dosed will be administered a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes). If a patient is re-dosed, a baseline anti-fXa activity sample will be drawn beforehand for central laboratory analysis; no post-initiation anti-fXa activity will be analyzed via local laboratory.

Table 2: Andexanet Dosing Paradigm and Criteria for Extended Treatment or Re-Dosing

Dose	Timing of Last Dose of FXa Inhibitor	Initial IV Bolus	Follow-On IV Infusion	Extended Infusion
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban 10 mg • Apixaban 5 mg • Enoxaparin 40 mg • Edoxaban 30 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes (480 mg total) irrespective of the duration of surgery	The infusion may be extended beyond 120 minutes at a rate of 4 mg/min (low-dose) for up to 4 additional hours.
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **> 15 hours or unknown time** • Local anti-fXa > 100 ng/mL (0.5 IU/mL for enoxaparin)	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes (960 mg total) irrespective of the duration of surgery	

a. Initial Bolus must be completed prior to start of surgery (initial skin incision).
b. Initial dosing (bolus + 120 min infusion) should be completely administered regardless of surgery length.
c. Infusion should continue throughout the duration of surgery, (defined as skin incision to skin closure).

Criteria for Extended Infusion

Extended Infusion (4 mg/min only) may continue up to an additional 4 hours to ensure continuous intraoperative infusion for the duration of surgery. The infusion may also continue through the immediate postoperative period at the Investigator's discretion.

Criteria for Re-Dosing with Andexanet

Consider re-dosing with andexanet (400 mg bolus + 4 mg/min infusion for 120 min) only if:

a. New, clinically significant, surgery-related, post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND
b. The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND
c. Re-dosing initiation occurs within 12 hours after the completion of the surgical procedure.

FXa = Activated factor X; IV = Intravenous.

6.3. Storage

The labeled storage condition for andexanet is refrigerated, (i.e., 2-8°C). The temperature of the medicine refrigerator should be monitored with an electronic temperature monitoring device.

6.4. Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write at least the date dispensed, dose dispensed, lot or batch code, person dispensing, and the patient's identification number on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record.

All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to Portola Pharmaceuticals, Inc. or its designee only after written authorization is obtained from Portola or its designees. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 13.5.

7.0 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1. Prior Medications and Treatments

See Section 4.1 and Section 4.2 for restrictions on prior medications and treatments.

7.2. Concomitant Medications, Hemostatic, and Procoagulant Treatments

7.2.1. Anticoagulants and Antiplatelet Drugs

Investigators may choose to re-start anticoagulants or antiplatelet drugs (including, but not limited to prasugrel, ticagrelor, clopidogrel, aspirin, and non-steroidal anti-inflammatory drugs) at any time based on clinical judgment. If anticoagulants or antiplatelet agents are restarted during the study, the date, time, dose, and agent(s) used should be recorded on the eCRFs. Heparin-based products deemed to be necessary per the Investigator's judgement (such as for postoperative DVT prophylaxis) may be started at any time. However, it should be noted that any agent with anti-fXa properties may be suboptimally effective when administered within 1 hour after cessation of andexanet infusion, as this time interval represents the effective $t_{½}$ of the drug.

7.2.2. Blood Products

To maintain uniformity in transfusion practices across study participants, it is strongly suggested that the trigger for PRBC transfusion is hemoglobin ≤ 8.0 g/dL (± 1 g/dL). The hemoglobin triggering a transfusion, clinical stability factors (e.g., shock) influencing the decision to transfuse, as well as the number of units transfused should be recorded on the eCRFs.

Whole blood and platelet transfusions may be administered according to standard institutional/local practices and/or guidelines. Investigators may consider using pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, fresh frozen plasma [FFP]) per their judgement in case of hemodynamic necessity. Otherwise, treatment with the above products is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of procoagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) and whole blood intraoperatively will result in the patient being considered having poor hemostatic efficacy (see Table 3) with andexanet.

Use of blood products, including number of units transfused and the date and time of administration should be recorded on the eCRFs.

7.2.3. Hemostatic Agents

Investigators may consider using systemic anti-fibrinolytic (e.g., aminocaproic acid and TXA) and other systemic hemostatic agents if a patient is found to require further hemodynamic

support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Similarly, local hemostatic agents (e.g., microfibrillar collagen and chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) may be used if a patient is found to require further hemodynamic support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of hemostatic agents, their dose, and the date and time of administration should be recorded on the eCRFs.

7.3. Post-Surgical Bleeding and Rescue Therapy

In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated during surgery, due to post-surgical bleeding events.

Investigators will therefore be allowed to deliver a second dose of andexanet (low-dose bolus + 120 minute infusion only) as rescue therapy should such a situation arise. If rescue re-dosing is deemed necessary, Investigators will be required to document in the eCRF the clinical justification for why subjects require additional dosing of andexanet. Study procedures will mirror those required for the initial andexanet dosing. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for re-dosing are outlined in Section 6.2. If a patient is confirmed to have post-surgical bleeding by the EAC, then they will be considered to have poor hemostatic efficacy (irrespective of the treatment given for bleeding, if any).

In the event a patient continues or restarts bleeding even after re-dosing with andexanet (or does not meet the criteria for re-dosing), standard of care should be employed and appropriately captured on the eCRFs.

8.0 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

8.1. Infusion Reactions

As described in Section 1.4.6, mild to moderate infusion reactions have been reported in healthy subjects treated with andexanet. These infusion reactions have generally resolved without interruption of the infusion or medical intervention. In the event that the Investigator determines that intervention is warranted, consideration may be given to slowing the infusion rate, or temporary interruption of the dose followed by re-starting the infusion at a slower infusion rate. Treatment with diphenhydramine may also be considered.

8.2. Thrombotic Events

Patients will be monitored carefully for signs and symptoms of TEs (i.e., strokes, transient ischemic attacks, MIs, DVTs, PEs, arterial systemic embolisms) throughout the course of the study. Should a diagnosis of a TE be considered, it is expected that an appropriate evaluation will be performed (e.g., head computed tomography [CT]/magnetic resonance imaging [MRI], electrocardiogram [ECG]/cardiac enzymes, lower extremity ultrasound, pulmonary vascular imaging). Investigators are requested to consult the guidance listed in Appendix E when considering whether an event should be considered a TE and therefore be submitted for adjudication. All events submitted for adjudication will be formally considered a suspected TE. Both suspected TEs and TEs confirmed by adjudication will be monitored as safety endpoints.

9.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

9.1. Safety Parameters and Definitions

9.1.1. Adverse Events

According to the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which may or may not have a causal relationship with the treatment.

An AE can be any of the following:

- Unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related.
- Any newly occurring event or exacerbation of previous condition (e.g., increase in severity or frequency) since the administration of study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

9.1.2. Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Is fatal (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening means that, in the opinion of the Investigator or Study Sponsor, the patient/subject was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother who was exposed to study drug or where the father was exposed to study drug before conception.
- Is an important medical event. An important medical event is an event that may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe MI); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on the strict regulatory definitions listed above and serves as a guide for defining regulatory reporting obligations. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted serious criteria. Thus, severity and seriousness need to be independently assessed for each AE recorded on the AE eCRF.

9.1.3. Non-Serious Adverse Events of Special Interest

The AESIs for this study include the following:

- A thrombotic or embolic event of any severity

All AESIs, whether serious or non-serious, must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Non-serious AESIs must be entered on the AE eCRF with a check in the AESI box.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs (Section 9.1.1 for definition) are recorded on the AE eCRF and reported to the Sponsor in accordance with instructions provided in this section.

For each AE recorded on the AE eCRF, the Investigator will make an assessment of seriousness (Section 9.1.2), causality (Section 9.2.2), and severity (Section 9.2.3).

9.2.1. Adverse Event Reporting Period

To comply with regulatory requirements, all SAEs and non-serious AESIs, regardless of causality, that occur from the date of signing of the ICF until 30 days after the last study drug treatment, must be reported to Portola or its safety designee within 24 hours from Investigator

awareness of the event. Survival status and reason for death will be ascertained at the Follow-up Day 30 study visit.

Patients who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate eCRF through the Follow-up Day 30 visit.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported to Portola or safety designee. These pre-dose AEs will be collected on the AE eCRF and assessed as not related to study drug, but will be assessed for relationship to study procedures/tests and interventions.

After initiation of study drug, all TEAEs, regardless of relationship to study drug, will be reported until **30 days after the last dose of study drug**. Any SAE that occurs with an onset date later than 30 days after completion of the study and that the Investigator considers to be related to study medication must be reported to Portola or safety designee.

To report any SAEs, the SAE Report Form provided to the clinical study site must be completed with the available information. Non-serious AEs that are AESIs must be reported on the SAE form with the box for AESI checked. The information collected must include at minimum the following: patient number, study drug(s) received, the event term, the serious criteria met for the AE, a narrative description of the event, and an assessment by the Investigator of the severity/intensity of the event and relationship to study drug(s). The SAE report should be sent to Portola or safety designee within 24 hours of Investigator awareness. Follow-up information on the SAE should be sent promptly by the Investigator to Portola or safety designee when any additional relevant information about the SAE becomes known to the Investigator, or as requested by Portola or safety designee. Safety reporting contact information is located in the Study Reference Manual.

Portola will immediately notify the Investigator about important safety or toxicology information, including antibodies against FX or FXa identified in a patient treated with andexanet in any clinical study, as it becomes available. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) about new and relevant safety information regarding the study drug, including serious adverse drug reactions involving risk to human subjects, in accordance with the applicable policies. Certain countries (e.g., the Netherlands), require Portola to notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious

adverse drug reactions involving risk to human subjects. An unexpected event is one that is not listed by nature or severity in the Investigator's Brochure.

9.2.2. Assessment of Causal Relationship

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or re-introduction of study drug (as applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

The following categories should be used in the causality assessment of suspected adverse reactions:

Probable

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; and
- Was unlikely to have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Possible

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; but
- Could have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unlikely

The AE:

- Does not follow a reasonable temporal sequence from the time of study drug administration; and
- Was most likely produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated

- This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention other than bleeding control, or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality. Importantly, lack of efficacy does not necessarily constitute relatedness to study drug.

9.2.3. Assessment of Severity

The Investigator must determine the severity of the event according to the criteria below and the Investigator's clinical judgment. Severity describes the intensity of the AE.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living
Grade 4	Life-threatening consequence or urgent intervention indicated
Grade 5	Event resulted in death

9.2.4. Procedures for Recording AEs

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF. Avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in the event field on the AE eCRF.

All AEs spontaneously reported by the patient and/or in response to an open-ended question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate forms in the eCRF.

Only 1 AE term should be recorded in the event field on the AE eCRF. When possible, a unifying diagnosis, or signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as a "common cold" rather than listing each symptom separately.

9.2.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record tumor lysis syndrome rather than hypocalcemia, hyperkalemia, hyperuricemia, etc.). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.2.4.2. Adverse Events that are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

9.2.4.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE eCRF with the severity (intensity or grade) of the events recorded at the time the event is first reported.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs, or notes a change in severity or seriousness. Each recurrence of an AE should be recorded as a separate event on the AE eCRF. For example:

- If Grade 1 vomiting has worsened to Grade 2 five days after onset, the Grade 1 vomiting is resolved on the date when the severity changed, and Grade 2 vomiting is recorded as a new event on the eCRF with onset date reflecting the change in severity.

If non-serious event of neutropenia required hospitalization 5 days after onset, the event is resolved on the hospitalization date, and a new SAE of neutropenia is recorded on the eCRF with start date reflecting when the event required hospitalization

9.2.4.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE eCRF.

9.2.4.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms.

- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Is clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF (Section 9.2.4.3 provides details on recording persistent AEs).

9.2.4.6. Deaths

Death should be considered an outcome and not a distinct event. All deaths that occur during the protocol-defined AE period should be reported as SAEs, regardless of attribution to study drug. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept (e.g., septic shock) with a fatal outcome. When the event that led to death cannot be identified (e.g., death of unknown origin) report "unexplained death" as the AE and update it when new information clarifies the event that led to death. Only 1 AE can be reported with a fatal outcome for each patient who dies. Other AEs that continued up to time of death should be reported with an outcome of not recovered/resolved. In the event that the death is attributed solely to natural progression of the underlying bleeding, the event is not reportable and should not be recorded as an AE.

9.2.4.7. Preexisting Medical Conditions

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE form, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.2.4.8. Hospitalization or Prolonged Hospitalization

The following hospitalizations are not considered SAEs in this clinical trial:

- Admissions per protocol for a planned medical/surgical procedure. Planned hospital admissions or planned surgical procedures for an illness or disease that existed before the patient was enrolled in the trial or before study drug was given are not to be considered

AEs, unless they occur at a time other than the planned date for a reason such as a worsening of the underlying disease/illness/symptoms.

- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.

Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

9.2.4.9. Pregnancy Exposure and Birth Events Reporting

Andexanet is not expected to have reproductive or developmental toxicity based on the following:

- Andexanet is intended for single-dose administration and, therefore, has limited potential for reproductive or developmental toxicity.
- Andexanet is a biotechnology-derived protein that is a modification of an endogenous protein in the coagulation cascade (FXa).
- Andexanet has a very short $t_{½}$ (1–2 hour effective $t_{½}$).
- Andexanet was designed as a universal antidote for FXa inhibitors, which are prescribed primarily in elderly patient populations that are not of reproductive capacity.

However, it is recommended that women of childbearing potential must use 2 medically acceptable methods of contraception, at least 1 of which must be a barrier method (e.g., non-hormone containing intra-uterine device plus condom, spermicidal gel plus condom), through at least 1 month following study drug dose.

Additionally, men with sexual partners of childbearing potential must use 2 acceptable methods of contraception, at least 1 of which must be a barrier method (e.g., spermicidal gel plus condom), for the entire duration of the study and for at least 1 month following study-drug; and men must refrain from attempting to father a child or donating sperm in the month following the study-drug.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a female study patient becomes pregnant or a female partner of a male study patient suspects she is pregnant, the Investigator should be informed immediately. Portola must, in turn, also be notified by the Investigator immediately by completing a Pregnancy Form. If a female partner of

a male study patient is pregnant or suspects she is pregnant, the male patient will be advised by the study Investigator to have his pregnant partner inform her treating physician immediately. The pregnancy must be followed up through delivery or other fetal outcome and information reported on a Pregnancy Follow-up form. For any abnormal fetal outcome (including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth), the Investigator should promptly report the abnormal fetal outcome to the Sponsor on an SAE form.

10.0 STUDY ASSESSMENTS

Assessments, testing and treatment schedules are detailed in Appendix A. No reference to timing or frequency is described below.

10.1. Baseline Assessments

10.1.1. Informed consent

An IRB/EC approved informed consent will be administered prior to performing study specific procedures or assessments. Administering informed consent is a process and will be documented in source documents. The current IRB/EC version of the consent will be used.

10.1.2. Demographics

Demographics will record the age, sex, race and ethnicity of patients. Race will be recorded (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific, White), and ethnicity will be recorded as Hispanic or Latino or Non-Hispanic or Latino.

10.1.3. Medical History

Patients will have a detailed medical history completed as part of baseline assessments. Diagnosis, year of onset and status will be reported. Status will consist of an end date or documentation as ongoing for the condition. Diagnosis should be documented and not signs and symptoms. Events with current treatment will have the treatment recorded in concomitant medications and therapies.

10.1.4. Prior and Concomitant Medications

Patients will be asked about their current physician prescribed medications, over the counter medications and any herbal or nutritional supplements. The generic name is preferred for Electronic Data Capture (EDC) entry. The dose, posology, frequency, start and stop dates and the diagnosis for use will be recorded.

10.1.5. Anticoagulant Dose or Plasma Level

Patients will be asked about the brand, dose and time of last dose of their anticoagulant. For patients who received the last dose of FXa inhibitor more than 15 hours (or an unknown time) prior to start of surgery, a local anti-fXa activity level may be obtained to allow enrollment of patients with >100 ng/mL levels. See Section 10.2.1 below on details for this local testing.

10.1.6. American Society of Anesthesiologists Physical Status Classification (ASA PS)

The American Society of Anesthesiologist Physical Status Classification is used to evaluate and describe the general health of patients prior to use of anesthetics or prior to surgery. The ASA PS consists of 6 categories to describe a patient's physical status (Appendix F). It will be used to

describe the population enrolled in the trial. It is not an assessment of operative risk, and will not be repeated during the study.

10.1.7. Eligibility Assessment

Following completion of assessments and screening testing, the investigator will determine eligibility of the patient by comparing results to inclusion and exclusion criteria. Note: it is Portola Pharmaceuticals Policy not to grant exceptions or waivers for inclusion and exclusion criteria.

10.1.8. Patient Identification Numbers

Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have signed informed consent and met the inclusion and exclusion criteria.

10.2. Central Laboratory Testing

Details on the collection, processing, storage, and shipment of samples are contained in the Laboratory Manual.

10.2.1. Anti-fXa Activity

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

Local laboratory anti-fXa activity testing may be utilized additionally by sites to ascertain eligibility (>100 ng/ml) if the time of last dose of FXa inhibitor is greater than 15 hours (or unknown). Local laboratory testing post-andexanet administration should be done with caution due to potential invalidity of local lab results from excessive sample dilution.

10.2.2. Thrombin Generation

Thrombin generation will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Thrombin generation will be measured using a tissue factor (TF)-initiated TG assay. This assay will be performed at a Central Laboratory. Five parameters related to TG are measured: endogenous thrombin potential (ETP), peak height, time to peak height, lag time and velocity index. Endogenous thrombin potential is prospectively identified as the primary measure for TG.

10.2.3. Tissue Factor Pathway Inhibitor

The TFPI activity will be measured using plasma samples in a Central Laboratory using a validated assay. The TFPI functional activity will be determined using a commercial kit. The assay measures FXa chromogenic activity following FX activation by factor VIIa/TF added to

the plasma. The TFPI activity is quantified by using a TFPI standard with U/mL as the readout. Binding of andexanet to TFPI will reduce the TFPI activity readout.

10.2.4. Anti-IIa Activity

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

10.2.5. Antibody Testing

Determination of the possible presence of antibodies to FX (human) and FXa (human) will be done at specific time points (see Appendix A) using the modified Bethesda assay. Antibodies against andexanet and HCPs will be assessed using standard immunogenicity assays.

For any sample that is positive for antibodies against andexanet, the potential for nAb activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a Central Laboratory.

10.3. Safety Assessments (other than Adverse Events)

10.3.1. Vital Signs

Vital signs include temperature (˚C), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (mmHg), heart rate (beats per minute), and respiratory rate (respirations per minute).

10.3.2. Physical Examination

A physical examination will be performed on all patients at various time points before and after the surgical procedure. The examination will include, at a minimum, any component relevant to the indication for surgery (e.g., abdominal examination for appendicitis, hip examination for hip fracture, neurologic examination for spinal cord compression) and an assessment of the surgical incision site (post-operative only).

10.3.3. Weight

Patient weight will be recorded in kg according to the schedule of assessments in Appendix A.

10.3.4. Clinical Laboratory Testing

Blood specimens for routine chemistry and hematology will be obtained at selected time points (see Appendix A).

The following assays will be performed at the Local Laboratory:

- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, WBC differential
- Coagulation: prothrombin time reported as the INR

- Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin
- Serum or urine pregnancy test (in women of child bearing potential; see Appendix D)

10.3.5. Optional Local Laboratory Testing of Anti-fXa Levels

Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion criteria. Further details and guidance on the conduct of local laboratory anti-fXa assays can be found in the Laboratory Manual for ANNEXA-S. Investigators are discouraged from evaluating anti-fXa activity with local assays after the administration of andexanet, due to the known inaccuracy of post-andexanet results caused by the large sample dilutions associated with unmodified commercial anti-fXa assays; however, if such testing is deemed necessary, it is strongly recommended that the procedures outlined in the Laboratory Manual be followed.

10.4. Intraoperative and Hospitalization Assessments

10.4.1. Surgical Intervention

All patients entering the trial are required to have an urgent need for surgical intervention. Institutional or procedural consents should be administered for the surgical intervention in accordance with local requirements and in addition to the study specific informed consent.

- The start of surgery is the initial incision.
- The end of surgery is final skin closure.

10.4.2. Intraoperative Blood Loss

Investigators will report blood loss during surgery for each patient. Blood loss will be reported as an estimate of blood loss in milliliters. Blood loss will be reported at the end of surgery. It is an intraoperative assessment and will not be updated for post-closure blood loss.

10.4.3. Assessment of Intraoperative Hemostasis

Intraoperative hemostasis will be captured as an investigator assessment. Categories for assessment are provide in Table 3 (Section 11.5.1).

10.4.4. Blood Products and Hemostatic Treatments

Blood products and hemostatic treatments employed as treatment prior to, during and postoperatively will be recorded. The product (generic), dose, route of administration, date and time of use will be recorded along with the reason for use.

10.4.5. Bleeding-related Diagnostic and Therapeutic Procedures

Any diagnostic and/or therapeutic procedures employed prior to, during and postoperatively will be recorded. For diagnostic procedures, the procedure, date, time, results and relevant units or description of results will be captured. Therapeutic procedures will be captured and concomitant medications/treatments with date, time, and posology (if applicable).

As a concomitant treatment, Investigators will record the product (generic name), date, time, indication and posology of colloid or crystalloid treatments used to support hemodynamic status.

10.4.6. Record Hours in Hospital Care Units

Investigators will record the date and time of entry into each care unit of the hospital. The date and time of entry and exit for each unit will be reported. This will be locally variable, but categories should be reconciled to the standards below:

- Emergency Department (ED): a unit dedicated to medical and surgical patients in need of immediate care.
- Intensive Care/Critical Care Department (ICU): a specialty medical unit for patients that are seriously ill are maintained under constant medical observation.
- Operating Room (OR): the room where the surgical procedure actually takes place.
- Post-anesthesia Care Unit (PACU): a specialty unit for providing post-anesthesia care for patients recovering from anesthesia.
- General Hospital Department or General Surgical Department: Covers a wide range of types of surgery and procedures on patients.

10.5. End of Study Assessments

Patients will have their survival status reported on the Day 30 or End of Study visit. This assessment will record the patient's status as alive or provide the date, time and cause of death. Note: see Section 9.0 for AEs reported for all deaths.

11.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study objectives and study design are described in Sections 2.0 and 3.1, respectively. The information in this section is a summary of the planned statistical analyses. Further details will be provided in the detailed Statistical Analysis Plan.

11.1. General Considerations

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

All hypothesis tests will be 2-sided and reported at the 0.05 significance level. All confidence intervals (CIs) will be 2-sided and reported at the 95% confidence level.

11.2. Randomization

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

11.3. Analysis Populations

11.3.1. Enrolled Population

The enrolled population will consist of all patients enrolled (signed informed consent and met inclusion/exclusion criteria) into the study irrespective of whether they received andexanet or not.

11.3.2. Safety Analysis Population

The safety analysis population will consist of all patients enrolled and treated with any amount of andexanet.

11.3.3. Efficacy Analysis Population

The efficacy analysis population will include all enrolled patients who receive any amount of andexanet treatment, undergo surgery, and have a baseline anti-fXa activity analyzed by central laboratory at or above the evaluability threshold (75 ng/mL for apixaban, edoxaban and rivaroxaban, and 0.25 IU/mL for enoxaparin).

11.4. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized for all populations listed above. Data will be summarized using descriptive statistics of frequencies for categorical data and means, medians, standard deviations, minimums, and maximums for continuous data. No inferential analyses of these data are planned.

11.5. Efficacy Endpoints and Analyses

11.5.1. Definitions

Hemostasis will be assessed from the start of surgery to the end of the procedure. Categories for the assessment of intraoperative hemostasis are provided in Table 3.

Table 3: Intraoperative Hemostasis Categories

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

* Tranexamic acid excluded.

The evaluation period for anti-fXa activity covers the period of time from 5 minutes following the end of the andexanet bolus to just prior to the end of the andexanet infusion. The baseline measurement will be the last value obtained prior to andexanet treatment.

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

11.5.2. Efficacy Endpoints

11.5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of effective hemostasis, as determined by the surgeon's assessment of intraoperative hemostasis and confirmed by adjudication by an independent EAC (see Table 3).

For each patient, hemostasis will be considered to be effective if the intraoperative hemostasis category is Excellent or Good, and ineffective if the intraoperative hemostasis category is Moderate or Poor.

A patient will be deemed non-evaluable if s/he meets the criteria specified in the EAC Charter.

11.5.2.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion.

Patients who do not have at least 1 anti-fXa activity level within the evaluation period will have percent decrease imputed as 0.0% (i.e., using the baseline value as the nadir value).

11.5.2.3. Exploratory Efficacy Endpoints

The following efficacy endpoints will be analyzed as exploratory:

- Relationship between intraoperative hemostasis and anti-fXa activity.
- Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, number of patients with percent reduction from baseline > 80%.
- Reversal of anticoagulant effect as measured by TG parameters (with ETP as the primary measure).
- Occurrence of receiving 1 or more RBC transfusions from start of the andexanet bolus through 12 hours after the end of surgery.
- The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the end of surgery.
- The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the end of surgery.
- Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the end of surgery.
- Time from the signing of informed consent to the start of surgery.
- Time from clinical presentation at treatment facility to the start of surgery.
- Length of index hospitalization, assessed at the Day 30 visit.
- Time hospitalized in a PACU, assessed at the Day 30 visit.
- Time hospitalized in an ICU, assessed at the Day 30 visit.
- Length of surgery.
- Total time in OR.
- Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post enrollment).
- Occurrence of post-surgical major bleeding, as defined by ISTH criteria (see Section 4.1), within 12 hours after the end of the initial surgery.
- Occurrence of re-operations for bleeding, including for surgical wound hematomas, within 12 hours after the end of the initial surgery.
- Change from baseline in TFPI activity post-administration of andexanet.
- Change from baseline in anti-IIa activity (only patients taking enoxaparin).

11.5.3. Statistical Methodology for Endpoint Analyses

All efficacy analyses will be performed on the efficacy analysis population. All hypothesis tests and CIs will be 2-sided with α=0.05.

The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI.

The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median.

For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.

11.6. Determination of Sample Size

Approximately 200 patients will be enrolled. After accounting for 10 to 25% attrition (e.g., canceled surgeries, discontinued and/or non-evaluable patients, or baseline anti-fXa activity analyzed by central laboratory less than the evaluability threshold), a sample size of 150 or 180 patients will provide an estimate of the proportion of achieving effective (excellent or good) hemostasis with a margin of error (half width of the 95% confidence interval) that is less than 8% or 7.3%, respectively. Additionally, with 150 to 180 patients, there will be 78% to 84% chance to observe a rare event with 1% occurrence rate.

11.7. Safety Endpoints and Summaries

Safety will be assessed by examining the following endpoints and analyzed in the Safety Analysis Population:

- AEs (including SAEs), vital signs, physical examinations, and clinical laboratory measurements.
- TEs within 30 days of enrollment, including those suspected and confirmed by adjudication.
- Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality.
- Antibodies to FX, FXa, andexanet, and HCPs.

11.7.1. Adverse Events

Treatment-emergent adverse events, including preferred terms defined by the Medical Dictionary for Regulatory Activities (MedDRA), will be summarized by system organ class. Arterial and venous thromboembolic events, considered AESIs, will be summarized separately.

The number of events, the number of patients, and the percentage of patients who experienced at least 1 TEAE will be presented. The TEAEs that are considered by the Investigator to be related to the andexanet, TEAEs that lead to early withdrawals, and serious TEAEs will be summarized in the same manner. Frequent TEAEs, including preferred terms with an incidence rate of ≥ 5%, will also be summarized.

All potential post-surgical bleeding events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event. Postoperative major bleeding events will be additionally adjudicated by the EAC.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

11.7.2. Thrombotic Events

All TEs will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event.

11.7.3. Deaths

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

11.7.4. Laboratory Parameters

Clinical laboratory parameters performed at the Central Laboratory (e.g., anti-fXa activity and TG) will be summarized by time point. For patients with anti-fXa activity levels obtained by a local laboratory assay for purposes of eligibility (for patients with a time from last dose greater than 15 hours), values will be documented but not formally analyzed.

Baseline values, the values at each subsequent visit, and changes from baseline will be summarized for each of the quantitative laboratory assessments.

11.7.5. Vital Signs

Vital signs will be summarized using actual values and change from baseline at pre-specified time points for each treatment group. Descriptive statistics, including threshold-based outlier analyses, will be presented.

11.7.6. Physical Examinations

Findings on physical examination will be summarized in a listing.

11.7.7. Antibodies

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

11.8. Interim Analyses

During the conduct of the study, interim monitoring of safety data by the DSMB will commence after 50 patients are enrolled, then performed periodically at a frequency of approximately every 6 months. Additional interim analyses of efficacy and/or safety data may be performed during the study to support regulatory and/or business objectives (such as informing future study designs). No adjustment to the type I error rate or CI coverage will be made to account for interim analyses. Details of the interim analysis and its review process will be described in the DSMB Charter.

11.9. Subgroup Analyses

Consistency of efficacy across important subgroups will be investigated within each cohort. At a minimum, primary efficacy will be summarized for subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, baseline anti-fXa activity categories (e.g., above and below thresholds of 30 ng/mL, 50 ng/mL, 75 ng/mL), procedure type (e.g., orthopedic, abdominal, thoracic, neurosurgical), duration of surgery (≤ 2 hours, 2-4 hours, > 4 hours), and volume of blood loss (above and below the median). Other subgroup analysis may be considered based on the actual enrollment. Further detail of the subgroup analysis will be described in the Statistical Analysis Plan.

12.0 STUDY COMMITTEES AND COMMUNICATIONS

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

- **Independent EAC**: Adjudication of hemostatic efficacy, deaths, TEs, and post-surgical bleeding events for all patients. The EAC will be blinded to all anti-fXa levels.
- **Independent DSMB**: Monitoring of all safety data.

13.0 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1. Institutional Review Board or Independent Ethics Committee

The protocol and ICF for this study must be reviewed and approved by an appropriate IRB or IEC before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, ICH, GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by Portola Pharmaceuticals, Inc. before initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or IEC, and to Portola Pharmaceuticals, Inc.

13.2. Informed Consent

Each patient must be provided with oral and written information describing the nature and duration of the study, and the patient must sign a written ICF in a language in which he/she is fluent before study-specific procedures are conducted. The signed and dated ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF. Due to the critical nature of the illness under study and the possibility that patients will be unable to provide their own consent, proxy consents (defined as consent from a legally authorized representative) and/or emergency consents (defined as consent from a qualified medical professional) are allowed if permissible by local or regional laws and regulations.

13.3. Documentation

The Investigator must provide Portola Pharmaceuticals, Inc. with the following documents (copies of which must be maintained by the Investigator):

1. Curriculum vitae of the Investigator and any sub-investigators listed on the Form FDA 1572.
2. A signed copy of the IRB or IEC approval notice for protocol and informed consent.
3. A copy of the IRB- or IEC-approved ICF.
4. Laboratory certification with a list of normal values for laboratory tests that will be conducted at local laboratories.
5. Completed financial disclosure form for the Investigator and any sub-investigators listed on the Form FDA 1572.

13.4. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant EDC system, as appropriate. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Some clinical laboratory data will be collected externally from the EDC systems. Further details for data collection and data handling will be specified in the data management plan, eCRFs, instructions for completing forms, other data handling procedures, and procedures for data monitoring. The MedDRA coding dictionary will be used for coding AEs, medical history conditions, and procedures. The reconciliation of the SAEs between the clinical and safety databases will be conducted as specified in plans determined and approved prior to study start-up. The WHO-DD dictionary will be used to code medications.

13.5. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.6. Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Portola Pharmaceuticals Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate eCRF. Deviations due to non-compliance that render subject non-evaluable for key endpoints will be considered significant deviations. Any other changes in the protocol will be made as an amendment to the protocol and must be approved by Portola Pharmaceuticals, Inc. and the IRB or IEC — before the changes or deviations are implemented.

Portola Pharmaceuticals, Inc. will not assume any responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol.

13.7. Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the US FDA and the study sponsor, Portola Pharmaceuticals, Inc., and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential.

13.8. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates andexanet was received from Portola and prepared for the study, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies can be destroyed at the site if available, in accordance with approved written procedures, or returned to Portola Pharmaceuticals, Inc. after written authorization is obtained from Portola Clinical Development. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 13.5.

13.9. Study Monitoring

The Investigator will allow representatives of Portola Pharmaceuticals, Inc. to periodically review (at mutually convenient times before, during, and after the study has been completed) all eCRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents, including documents that support patients' eligibility (e.g., medical history, concomitant medications) should be made available to the study monitor. The monitoring visits provide Portola Pharmaceuticals, Inc. with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

14.0 REFERENCES

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15.0 LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ACTIVITIES

	Screening & Baseline			Treatment				Follow-Up		
STUDY DAY:	1							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW:	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**End of Bolus** +15 min	**EoII -15 min**	**EoS [1]** + 15 min [2]	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Obtain Consent	X									
Determine Eligibility	X									
Obtain Medical History	X									
Demographics	X									
Obtain Prior Medications and Time of Last Anticoagulant Dose or Plasma Level	X									
Obtain ASA Class			X							
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X	X	X	X	X
Weight (actual reported/recent)	X									X
Physical Examination	X						X	X	X	X
Central Labs: Anti-fXa and anti-IIa Activity		X (pre-ADX)		X	X	X	X			
Central Labs: Thrombin Generation		X (pre-ADX)		X	X	X	X	X	X	
Central Labs: Antibodies to andexanet, HCPs, and FX/FXa (modified Bethesda); and nAb (andexanet)	X (pre-ADX)									X
Central Labs: TFPI activity		X (pre-ADX)		X	X	X	X	X	X	X
Local Labs: PT-INR	X									

	Screening & Baseline		Treatment					Follow-Up		
STUDY DAY:	**1**							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW:	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**End of Bolus** +15 min	**EoII -15 min**	**EoS [1]** + 15 min [2]	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Local Labs: Chemistry and Pregnancy Test [3]	X									
Local Labs: CBC		X				X	X			X
Prepare Andexanet	X									
Administer Andexanet Bolus, Immediately Followed by an Infusion			**X**							
Assess Need for Extended Andexanet Infusion.(if Surgery Ongoing)					X [4]					
Surgical Intervention				SURGERY						
Record Blood Loss Post Surgery						X				
Record Investigator Assessment of Intraoperative Hemostasis						X				
Record Blood Products & Hemostatic Treatments [5]		X								
Record Bleeding-Related Diagnostic & Therapeutic Procedures [6]		X						X	X	
Record Volume of Colloid and Crystalloid [5]		X								
Record Hours in ED, PACU, ICU/Critical Care, General Hospital Floor, and Total as an Inpatient										X

	Screening & Baseline			Treatment				Follow-Up		
STUDY DAY:	**1**							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW:	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**End of Bolus** +15 min	**EoII -15 min**	**EoS [1]** + 15 min [2]	**EoS + 12 h** ± 1 h	**EoS + 24 h** ± 1 h	**EoS + 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Record AEs	X	X						X	X	X
Record Concomitant Medications	X	X						X	X	X
Ascertain Survival Status										X

ADX = andexanet; AE = Adverse event; ASA = American Society of Anesthesiologists; BP = Blood pressure; CBC = Complete blood count; ED = Emergency department; EoII = End of Initial Infusion; EoS = End of Surgery; ET = Early Termination; FX = Factor X; FXa = Activated factor X; h = Hour(s); HCP = Host-cell protein; HR = Heart rate; ICU = Intensive care unit; INR = International normalized ratio; min = Minute(s); nAb = Neutralizing antibody (activity); OR = operating room; PACU = Post-anesthesia care unit; PT = Prothrombin time; RR = Respiratory rate; SoS = Start of Surgery; Temp = Temperature; TFPI = Tissue factor pathway inhibitor

[1] The EoS time point before may occur SoS + 1 hour or SoS + 2 hour; EoS procedures should be carried out when EoS occurs.

[2] Collect EoS samples within 15 minutes from the end of surgery but before stopping infusion.

[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.

[4] Approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

[5] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.

[6] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.

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

APPENDIX B. DISSEMINATED INTRAVASCULAR COAGULATION (DIC) SCORING ALGORITHM [8]

Note: Algorithm should only be used for patients with an underlying disorder known to be associated with overt DIC. A score of ≥ 5 is compatible with overt DIC.

Laboratory Test	Result	Score
Platelet Count	≥ 100 x 10^9 / L	0
	< 100 x 10^9 / L	1
	< 50 x 10^9 / L	2
D-Dimer, Fibrin Degradation Products	No increase	0
	Moderate increase	2
	Strong increase	3
Prothrombin Time	< 3 seconds	0
	≥ 3 but < 6 seconds	1
	≥ 6 seconds	2
Fibrinogen Level	≥ 1 g/L	0
	< 1 g/L	1

APPENDIX C. DEFINITIONS OF CARDIOGENIC SHOCK, SEVERE SEPSIS AND SEPTIC SHOCK [9]

Cardiogenic shock is a cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion [10]. The definition of cardiogenic shock may be clinically determined and consists of the following: Systolic blood pressure (SBP) < 90 mmHg for at least 30 minutes, OR

- Hemodynamic support required to maintain SBP ≥ 90 mmHg, AND
- End-organ hypoperfusion (e.g., urine output < 30 mL/hr or cool extremities)

Cardiogenic shock may also be optionally defined by hemodynamic criteria obtained through invasive hemodynamic monitoring:

- Cardiac index ≤ 2.2 L/min/m^2, AND
- Pulmonary capillary wedge pressure ≥ 15 mmHg

Severe sepsis is defined as sepsis-induced tissue hypoperfusion or organ dysfunction with any of the following thought to be due to the infection:

- Sepsis-induced hypotension
- Lactate above upper limit of normal (ULN)
- Urine output < 0.5 mL/kg/hr for more than 2 hours despite adequate fluid resuscitation
- Acute lung injury with partial pressure oxygen-arterial (PaO_2)/fraction of inspired oxygen (FIO_2) < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO2/FIO2 < 200 in the presence of pneumonia as infection source
- Creatinine > 2 mg/dL (176.8 micromol/L)
- Bilirubin > 4 mg/dL (34.2 micromol/L)
- Platelet count < 100,000 $microL^{-1}$
- Coagulopathy (International normalized ratio [INR] > 1.5)

Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.

Sepsis-induced hypotension is defined as a SBP < 90 mmHg, or mean arterial pressure (MAP) < 70 mmHg, or a SBP decrease > 40 mmHg, or less than 2 standard deviations below normal for age in the absence of other causes of hypotension.

Septic shock is defined as sepsis-induced hypotension (as defined above) persisting despite adequate fluid resuscitation.

APPENDIX D. DEFINITION OF FEMALE OF CHILDBEARING POTENTIAL

All women of childbearing potential (including those who have had a tubal ligation) will have a urine or serum pregnancy test at screening. If the pregnancy test is positive, andexanet should not be administered.

All female patients are considered to be of childbearing potential unless they meet 1 of the following criteria:

1. The patient has been post-menopausal (amenorrheic) for at least 1 year
2. The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to screening
3. The patient had a hysterectomy

APPENDIX E. GUIDANCE FOR SUBMISSION OF POTENTIAL THROMBOTIC EVENTS FOR ADJUDICATION

Adjudication criteria for the diagnosis transient ischemic attacks, strokes, myocardial infarctions (MIs), venous thromboembolism, and arterial systemic embolism are provided below.

Transient Ischemic Attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with signs or symptoms lasting < 24 hours and no evidence of new infarct on neuroimaging if performed. Investigators should consider submitting cases for adjudication if an event meets this definition.

Stroke is defined as an acute episode of neurological dysfunction consistent with a vascular cause. A stroke will be considered to have occurred if there is a rapid onset of signs and/or symptoms of a new persistent neurological deficit consistent with an obstruction to cerebral blood flow with no apparent nonischemic cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours or, for symptom onset less than 24 hours, have neuroimaging evidence of new infarct. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. For the diagnosis of stroke, the following criteria must be fulfilled:

- Rapid onset of a focal/global neurologic deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphagia/aphasia, hemianopia, amaurosis fugax, or other new neurological signs/symptoms consistent with stroke.
- The duration of a focal/global neurologic deficit is at least 24 hours, OR the neurological deficit results in death, OR there is neuroimaging evidence of a new infarct.
- There is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion).
- Confirmation of the diagnosis by at least 1 of the following: specialist evaluation, or brain imaging procedure (i.e., computed tomography [CT] scan, magnetic resonance imaging [MRI] scan, cerebral vessel angiography).

If the acute neurological signs represent a worsening of a previous (baseline) deficit, the new signs must have either persisted for more than 1 week, or persisted for more than 24 hours and were accompanied by an appropriate new imaging finding.

Investigators should consider submitting cases for adjudication as a possible stroke if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., delirium, mental status changes) that are not otherwise explainable by an alternative etiology.

Since the adjudication of hemostatic efficacy encompasses changes in clinical neurologic function and hematoma volume, these findings will only be considered for thrombotic event adjudication if they clearly have an ischemic etiology.

Myocardial Infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis of MI:

- Detection of a risk and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the upper limit of normal (ULN) and with at least 1 of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block
  - Development of pathological Q waves in the electrocardiogram (ECG)
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new left bundle branch block (LBBB), but death occurred before biomarkers were obtained, or before cardiac biomarker values would be increased
- Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (> 5 × ULN) in patients with normal baseline values or a rise of cTn values> 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic ECG changes, (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the ULN
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 × ULN) in patients with normal baseline cTn values. In addition, either (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Investigators should consider submitting cases for adjudication as a possible MI if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., angina,

ventricular tachyarrhythmia, cardiogenic shock, heart failure) that are not otherwise explainable by an alternative etiology.

Venous Thromboembolism is defined as a symptomatic deep vein thrombosis (DVT) or PE confirmed by objective testing. Criteria for the objective confirmation of DVT include:

- A constant filling defect in 2 or more views on contrast venography in 1 or more proximal venous segments (iliac, common femoral, superficial femoral, popliteal)
- New or previously undocumented non-compressibility of 1 or more venous segments on compression ultrasound
- A clearly defined intraluminal filling defect on contrast enhanced CT

Criteria for the objective confirmation of PE include:

- An intraluminal filling defect on pulmonary angiography
- Sudden contrast cut-off of 1 or more vessels more than 2.5 mm in diameter on a pulmonary angiogram
- A high probability ventilation-perfusion (VQ) scan (1 or more segmental perfusion defects with corresponding normal ventilation)
- An abnormal non-high VQ scan plus criteria for the diagnosis of DVT
- An unequivocal, intra-arterial, un-enhancing filling defect in the central pulmonary vasculature (pulmonary trunk, main pulmonary arteries, anterior trunk, right and left interlobar and lobar arteries) on CT

Investigators should consider submitting cases for adjudication as a possible VTE if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., lower extremity swelling, respiratory failure) that are not otherwise explainable by an alternate etiology. All cases of unexplained sudden death should also be submitted for adjudication as a possible PE and/or MI.

Arterial systemic embolism is defined as abrupt vascular insufficiency associated with clinical and other objective evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs and symptoms must be consistent with embolic arterial occlusion, and there must be clear evidence of abrupt occlusion of a systemic artery, with at least 1 type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report. Investigators should consider submitting potential systemic arterial embolism cases for adjudication if they meet this definition.

APPENDIX F. AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION

ASA PS 1	Normal healthy patient
ASA PS 2	Patients with mild systemic disease
ASA PS 3	Patients with severe systemic disease
ASA PS 4	Patients with severe systemic disease that is a constant threat to life
ASA PS 5	Moribund patients who are not expected to survive without the operation
ASA PS 6	A declared brain-dead patient whose organs are being removed for donor purposes

ASA = American Society of Anesthesiology; PS = Physical Status

APPENDIX G. PROTOCOL SUMMARY OF CHANGES (ORIGINAL VS AMENDMENT 1)

First Section of Occurrence (& Throughout Document)	Old Text (From Original)	New Text (Strikethrough Indicates Deleted Text / Bold Italics Indicates Added Text)	Rationale for Revision	Substantial (S) or Non-substantial (NS) Change
Global	CRF	***e***CRF	All instances of "CRF" were replaced with "eCRF" for consistency and clarity.	NS
Title Page	Phase 3b/4	Phase 3~~b~~/4	Clarified phase.	NS
Investigator's Agreement	I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulation (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.	I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal ~~Regulation~~ ***Regulations*** (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.	Typo.	NS
Synopsis, Number of Sites	Approximately 120 sites in North America, Europe, and Rest of World	Approximately 120 sites in ~~North America, Europe, and Rest of World~~ ***Globally***	Language changed to be less restrictive.	NS
Synopsis, Objectives	**Exploratory Efficacy Objectives:** • To evaluate the effect of andexanet on thrombin generation (TG). • To evaluate the use of red blood cell (RBC) transfusions. • To evaluate the use of non-RBC, non-platelet blood products and hemostatic agents. • To evaluate the transfusion-corrected change in hemoglobin from baseline to	**Exploratory Efficacy Objectives:** • To evaluate the effect of andexanet on thrombin generation (TG). • To evaluate the use of red blood cell (RBC) transfusions. • To evaluate the use of non-RBC, non-platelet blood products and hemostatic agents. • To evaluate the transfusion-corrected change in hemoglobin from baseline to the	Language changed to add clarity.	NS

	the nadir. • To evaluate the time from obtaining informed consent to the start of surgery. • To evaluate the length of index hospitalization, intensive care unit (ICU) stay, and length of surgery. • To evaluate the occurrence of re-hospitalization. • To evaluate the occurrence of post-surgical bleeding, including surgical wound hematomas. • To evaluate the occurrence of re-operations for bleeding. • To evaluate the effect of andexanet on tissue factor pathway inhibitor (TFPI). • In patients receiving enoxaparin, to evaluate the effect of andexanet on anti IIa activity	nadir. • To evaluate the time from obtaining informed consent ***(study consent)*** to the start of surgery. • To evaluate the length of index hospitalization, intensive care unit (ICU) stay, ***time in a post-anesthesia care unit (PACU), time in the operating room (OR)***, and length of surgery. • To evaluate the occurrence of re-hospitalization. • To evaluate the occurrence of post-surgical ***major*** bleeding, ~~including surgical wound hematomas~~. • To evaluate the occurrence of re-operations for bleeding. • To evaluate the effect of andexanet on tissue factor pathway inhibitor (TFPI) ***activity***. • In patients receiving enoxaparin, to evaluate the effect of andexanet on anti IIa activity		
Synopsis, Efficacy Endpoints	**Exploratory Endpoints:** • Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, 12-hour nadir, number of patients with percent reduction from baseline > 80%. • Reversal of anticoagulant effect as measured by TG parameters (with endogenous thrombin potential as the primary measure). • Occurrence of receiving 1 or more RBC transfusions from the start of the andexanet bolus through 12 hours after the start of surgery.	**Exploratory Endpoints:** • ***Relationship between hemostatic efficacy and anti-fXa activity.*** • Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, ~~12-hour nadir,~~ number of patients with percent reduction from baseline > 80%. • Reversal of anticoagulant effect as measured by TG parameters (with endogenous thrombin potential as the primary measure). • Occurrence of receiving 1 or more RBC transfusions from the start of the andexanet	Additional endpoints added. Language modified to clarify timing in relation to surgery.	S

	• The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the start of surgery. • The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the startend of surgery. • Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the start of surgery. • Time from the signing of informed consent to the start of surgery. • Length of index hospitalization, assessed at the Day 30 visit. • Time hospitalized in an ICU, assessed at the Day 30 visit. • Length of surgery. • Occurrence of re-hospitalization, within 30 days of enrollment, including length of re hospitalization (through 30 days post enrollment). • Occurrence of post-surgical bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery. • Occurrence of re-operations for bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery. • Change from baseline in TFPI activity post-administration of andexanet. • Change from baseline in anti-IIa activity (only patients taking enoxaparin).	bolus through 12 hours after the ~~start~~ ***end*** of surgery. • The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the ~~start~~ ***end*** of surgery. • The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the ~~start~~ ***end*** of surgery. • Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the startend of surgery. • ~~Time~~ ***Length of time*** from the signing of informed consent to the start of surgery. • ***Length of time from clinical presentation at the treating facility to the start of surgery.*** • Length of index hospitalization, assessed at the Day 30 visit. • ***Time hospitalized in a PACU, assessed at the Day 30 visit.*** • Time hospitalized in an ICU, assessed at the Day 30 visit. • Length of surgery. • ***Time in the OR.*** • Occurrence of re-hospitalization, within 30 days of enrollment, including ***number of days*** and length of re hospitalization (through 30 days post enrollment). • Occurrence of post-surgical ***major*** bleeding, ~~including surgical wound hematomas~~ ***as defined by International Society on Thrombosis and Haemostasis (ISTH) criteria***, within 12 hours after the start of the initial surgery. • Occurrence of re-operations for bleeding, including surgical wound hematomas,		

		within 12 hours after the ~~start~~ ***end*** of the initial surgery. • Change from baseline in TFPI activity post-administration of andexanet. • Change from baseline in anti-IIa activity (only patients taking enoxaparin).		
Synopsis, Study Design	This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery who have within 15 hours received their last dose of 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. If the time from last dose of FXa inhibitor is unknown, the patient is not eligible. Alternatively, if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin), the patient may be enrolled, irrespective of the time of the last dose (even if unknown). The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have sufficient anti-fXa activity levels. The start of the andexanet bolus must be within 15 hours following the last dose of FXa inhibitor. Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an intravenous (IV) bolus administered over 15 to 30 minutes (depending on dose); the bolus will be followed by an IV infusion that will continue for 2 hours, irrespective of the duration of the surgery. The bolus	This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery, ***and*** who have, within 15 hours ***prior to surgery***, received their last dose of 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. If the time from last dose ~~of FXa inhibitor~~ is unknown, ***or greater than 15 hours prior to surgery,*** the patient ~~is not eligible. Alternatively,~~ ~~if~~ ***may be enrolled provided*** a local ***laboratory*** anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin). ***In such cases*** the ~~patient may be enrolled, irrespective of~~ ***start of surgery must begin no greater than 4 hours after*** the ~~time of~~ ***blood collection for*** the ~~last dose (even if unknown).~~***local anti-fXa activity test.*** The prespecified time periods and~~/or~~ anti-fXa activity ~~levels~~ ***level thresholds*** are designed to ensure patients have ~~sufficient~~ ***sufficiently high*** anti-fXa activity levels. ***Only patients with effective levels of anticoagulation will be included in the Efficacy Analysis Population. Accordingly, the Efficacy Analysis Population for the study will only include patients whose central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin).***	Clarify timing in relation to dosing and surgery. Include new tests/ assessments. Clarify which patients will be included in the Efficacy Analysis Population.	S

	will begin prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision; designated Time 0). Additional andexanet, be it for re-dosing or extended infusion, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-operative complications are met (see "Test Product, Dose, and Mode of Administration" below). .. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter. All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit.	The start of ~~the andexanet bolus~~ ***surgery*** must be within 15 hours following the last dose of FXa inhibitor. Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an intravenous (IV) bolus administered over 15 to 30 minutes (depending on dose) ***immediately prior to the start of surgery (skin incision). The bolus must be completely administered before the start of surgery (i.e., at the first incision; designated Time 0).*** ~~); the bolus will be~~ ***The bolus must be immediately*** followed by an IV infusion that will continue for 2 hours, irrespective of the duration of the surgery. ~~The bolus will begin prior to, but not more than 30 minutes before,~~ ***The infusion should continue from start to end of surgery (skin incision to skin closure*** ~~the start of surgery (i.e., at the first incision; designated Time 0). Additional andexanet, be it for re-dosing or extended infusion, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-operative complications are met (see "Test Product, Dose, and Mode of Administration" below~~). ***Additional andexanet, be it for extended infusion or re-dosing, may be given at the discretion of the Investigator when specific criteria are met (see "Test Product, Dose, and Mode of Administration" below). The treating surgeon will assess hemostatic efficacy at the conclusion of the procedure (i.e., skin closure).*** ... An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter.		

		All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. ***In addition, patients who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit.***		
Synopsis, Study Periods	The study duration for any individual patient will be up to 37 days. There are 4 study periods. Study periods are defined as follows: • Screening Period: < 1 day (Day 1). • Pre-surgical Assessment Period: < 1 day (Day 1). • Treatment Period: < 1 day (Day 1). o Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~2.5 hours) but no greater than a total 6 hours (including both the initial regimen and the extended infusion). o Re-Dosing < 1 day, Day 1 or 2 (initiation occurs within 24 hours after the completion of the first course of andexanet treatment if applicable.) • Safety Follow-up Period: 30 + 7 days (Days 1–30 + 7).	The study duration for any individual patient will be up to 37 days. There are 4 study periods. Study periods are defined as follows: • Screening Period: ~~< 1 day (~~Day 1~~)~~. • Pre-surgical Assessment Period: ~~< 1 day (~~Day 1~~)~~. • Treatment Period: ~~< 1 day (~~Day 1~~)~~. o Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~2.5 hours) but no greater than a total 6***.5*** hours (including both the initial regimen and the extended infusion). o Re-~~Dosing < 1 day, Day 1 or 2 (initiation occurs~~ ***dosing (low dose bolus and infusion) may occur*** within ~~24~~ ***12*** hours after ~~the~~ completion of the first course of andexanet treatment ~~if applicable.)~~ ***(but after the conclusion of the surgical procedure) if protocol specified criteria are met, at the investigators discretion***. • Safety Follow-up Period: ~~30 + 7 days~~ (Days 1–30 + 7).	Time frames changed to remove ambiguity. Language added to clarify timing of dosing in relation to surgery.	S
Synopsis, Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or their medical proxy (or legal designee) has given written informed consent. 2. Age ≥ 18 and < 85. 3. Requires urgent surgical intervention that	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or their medical proxy (or legal designee) has given written informed consent. 2. Age ≥ 18 and < 85 ***years old***. 3. Requires urgent surgical intervention that	Added assessment for anti-FXa activity level. Added clarification on	S

	must occur within 12 hours of clinical presentation, for which reversal of anti-fXa activity is judged necessary. 4. Received 1 of the following FXa inhibitors within 15 hours prior to start of surgery: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d), OR if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin), the patient may be enrolled, irrespective of the time of the last dose. 5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential). 6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).	must occur within 12 hours of ~~clinical presentation~~ ***consent***, for which reversal of anti-fXa activity is judged necessary. 4. Received 1 of the following FXa inhibitors ~~within 15 hours prior to start of surgery~~: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d), ~~OR if)~~ ***within 15 hours prior to start of surgery. If the time from the last dose is unknown or greater than 15 hours, the patient may be enrolled provided*** a local ***laboratory*** anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin~~), the patient may be enrolled, irrespective of the time of the last dose.~~). 5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential). 6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).	multiple inclusion criteria.	
Synopsis, Exclusion Criteria	If a patient meets any of the following criteria, he or she is not eligible: 1. Surgery predicted to last > 4 hours or for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low. 2. Acute life-threatening bleeding at the time of screening. 3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the intra-operative use of systemic, intravascular, unfractionated heparin. 4. Expected survival of < 1 month due to	If a patient meets any of the following criteria, he or she is not eligible: 1. Surgery ~~predicted to last > 4 hours or~~ for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low. 2. Acute life-threatening bleeding ***(ISTH criteria)*** at the time of ~~screening.~~ ***Screening***: a. ***The patient has acute-overt bleeding that is potentially life-threatening, e.g., with signs or symptoms of hemodynamic compromise, such as severe hypotension, poor skin perfusion, mental confusion, low urine output that cannot be otherwise***	Included additional exclusion criterion. Addressed typos.	S

	comorbidity. 5. Existing "Do Not Resuscitate" order or similar advanced directive. 6. The patient has a recent history (within 30 days prior to screening) of a diagnosed TE as follows: venous thromboembolism (including deep vein thrombosis, pulmonary embolism, intracardiac thrombus), myocardial infarction (including asymptomatic troponin elevations), disseminated intravascular coagulation, acute traumatic coagulopathy, cerebrovascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease. 7. Acute decompensated heart failure or cardiogenic shock at the time of screening. 8. The patient has severe sepsis or septic or severe hemorrhagic shock at the time of Screening. 9. The patient is pregnant or a lactating female. 10. The patient has received any of the following drugs or blood products within 7 days of enrollment: o Vitamin K antagonist (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (e.g., NovoSeven®). o Whole blood, plasma fractions. Note: Administration of tranexamic acid, platelets or packed red blood cells is not an exclusion criterion.	***explained.*** b. ***The patient has overt bleeding associated with a fall in hemoglobin level by ≥2g/dL, OR, a hemoglobin ≤8 g/dL if no baseline hemoglobin is available.*** ***c. The patient has acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal***. 3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the ~~intra-operative~~ ***intraoperative*** use of systemic, intravascular, unfractionated heparin. 4. ***Primary procedure for efficacy assessment is a non-surgical interventional procedure (e.g, lumbar puncture, skin biopsy, cardiac catheterization, endoscopic retrograde cholangio-pancreatography).*** ~~4.~~***5.*** Expected survival of < 1 month due to comorbidity. ~~5.~~***6.*** ~~Existing~~ ***Known*** "Do Not Resuscitate" order or similar advanced directive. ~~6.~~***7.*** The patient has a recent history (within 30 days prior to screening) of a diagnosed TE as follows: venous thromboembolism (including deep vein thrombosis, pulmonary embolism, intracardiac thrombus), myocardial infarction (including asymptomatic troponin elevations), disseminated intravascular coagulation, acute traumatic coagulopathy, cerebrovascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease. ~~7.~~***8.*** Acute decompensated heart failure or cardiogenic shock at the time of		

	11. The patient was treated with an investigational drug < 30 days prior to Screening. 12. Prior treatment with andexanet.	screening. ~~8~~***9.*** The patient has severe sepsis or septic or severe hemorrhagic shock at the time of Screening. ***10. The patient has heparin-induced thrombocytopenia (with or without thrombosis).*** ***11. Inherited coagulopathy (e.g., anti-phospholipid antibody syndrome, protein C/S deficiency, Factor V Leiden)*** ***12. Last dose of apixaban < 2.5 mg, rivaroxaban < 10 mg, edoxaban < 30 mg, or enoxaparin 40 mg.*** ~~9~~***13.*** The patient is pregnant or a lactating female. ~~10~~***14.*** The patient has received any of the following drugs or blood products within 7 days of enrollment: o Vitamin K ~~antagonist~~ ***antagonists*** (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (e.g., NovoSeven®). o Whole blood, plasma fractions. Note: Administration of tranexamic acid, platelets or packed red blood cells is not an exclusion criterion. ~~11~~***15.*** The patient was treated with an investigational drug < 30 days prior to Screening. ~~12~~***16.*** Prior treatment with andexanet.		
Synopsis, Test Product, Dose, and Mode of Administration	The andexanet IV bolus will be initiated within 30 minutes prior to the start of surgery (i.e., the first incision). The bolus will be followed by a continuous infusion lasting 120 minutes, irrespective of the	The andexanet IV bolus will be initiated within 30 minutes prior to the start of surgery (i.e., the first incision) ~~.~~ ***and must be completed prior to surgery start.*** The bolus will be followed by a continuous infusion	Clarified dosing and surgery details and timing. Clarified	S

	length of the surgery. It is possible that the bolus or continuous infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens as described below: <Table> **Extended Infusion** Following the primary andexanet bolus and infusion (~2.5 hours), the andexanet infusion will be continued at the low dose of andexanet (4 mg/min) if the surgery and immediate post-operative period extend longer than the primary bolus and infusion. The extended infusion will continue through the end of the surgery and the immediate post-operative period, not to exceed 6 hours total. **Criteria for Re-Dosing with Andexanet** Consider re-dosing with andexanet (low-dose bolus + infusion) only if: a) New, clinically significant, surgery-related post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b) The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c) Re-dosing initiation occurs within 12 hours after the start of the first course of andexanet treatment.	lasting ***at least*** 120 minutes, irrespective of the length of the surgery. ~~It is possible that the bolus or~~ ***The*** continuous infusion ~~may~~ ***must*** be ongoing at the start of surgery, ***and must continue until the end of surgery even if extended treatment is required***. There are 2 possible dosing regimens as described below: <Table> ***Extended Infusion** (**Additional low-dose 4 mg/min infusion up to 4 hours)*** Following the primary andexanet bolus and ***120-minute*** infusion ~~(~2.5 hours)~~, the andexanet infusion will be continued at the low dose of andexanet (4 mg/min) if the surgery ~~and immediate post-operative period extend~~ ***extends*** longer than the primary bolus and infusion. The extended infusion ~~will~~ ***(1) must*** continue ***at least*** through the end of the surgery and ***(2) may additionally continue during*** the immediate post-operative period, ***(per investigator discretion), and (3) should not*** ~~to~~ exceed ~~6~~ ***4*** hours. ***The total duration of dosing including initial bolus, 120-minute infusion, and any extended infusion, should not exceed 6.5 hours. The limit of planned duration of infusion is stipulated to balance declining anti-fXa plasma levels and acceptable exposure to andexanet.*** **Criteria for Re-Dosing with Andexanet** Consider re-dosing with andexanet (low-dose bolus + ***120 min*** infusion) only if: a) New, clinically significant, surgery-related post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b) The treating physician has clinical	criteria for re-dosing or extended infusion. For Table changes, see the end of this appendix.	

		suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c) Re-dosing initiation occurs within 12 hours after the ~~start~~ ***completion*** of ~~the first course of andexanet treatment.~~ ***surgical procedure.*** ***Maximum Length of Dosing (Initial Bolus + 120 minute Infusion + Extended Infusion, < 6.5 hours):***		
Synopsis, Sample Size	**Total Enrollment Approximately 200 Patients** It is estimated that a sample size of 180 patients will provide approximately 89% power to reject the null hypothesis that 67% of the patients will achieve effective hemostasis. This power calculation assumes the true rate of achieving effective hemostasis is 77%. An approximate 10% attrition rate is expected (e.g., canceled surgeries, discontinued and/or non-evaluable patients). Therefore, 200 patients will be enrolled.	~~Total Enrollment~~ Approximately 200 ~~Patients~~ ~~It is estimated that~~ ***patients will be enrolled. After accounting for 10 to 25% attrition (e.g., canceled surgeries, discontinued and/or non-evaluable patients, or baseline anti-fXa activity analyzed by central laboratory less than the evaluability threshold),*** a sample size of ***150 or*** 180 patients will provide ~~approximately 89% power to reject the null hypothesis that 67%~~ ***an estimate*** of the ~~patients will achieve effective hemostasis. This power calculation assumes the true rate~~ ***proportion*** of achieving effective ~~hemostasis is 77%. An approximate 10% attrition rate is expected (e.g., canceled surgeries, discontinued and/or non-evaluable patients). Therefore, 200~~ ***(excellent or good) hemostatic efficacy with a margin of error (half width of the 95% confidence interval) that is less than 8% or 7.3%, respectively. Additionally, with 150 to 180*** patients ~~will be enrolled.~~ ***, there will be 78% to 84% chance to observe a rare event with 1% occurrence rate.***	Revised language to account for possible attrition rates and rare events.	S
Synopsis, Statistical Analysis Methods for Efficacy	All efficacy analyses will be performed in the Efficacy Analysis Population. All hypothesis tests and confidence intervals (CI) will be 2-sided with α=0.05. The primary endpoint, the proportion of	All efficacy analyses will be performed in the Efficacy Analysis Population. All hypothesis tests and confidence intervals (CI) will be 2-sided with α=0.05. The primary endpoint, the proportion of	Removed null and alternative hypotheses testing.	S

	patients who have effective hemostasis, will be summarized with a 95% CI. The null and alternative hypotheses tested to support this analysis are: H0: $\pi = 0.67$ H1: $\pi \neq 0.67$ The study will be considered to have met its primary efficacy objective if the proportion of patients with effective hemostasis is statistically significantly higher than 67% ($p < 0.05$) using a 2-sided Chi-Square test with $\alpha = 0.05$, or the lower bound of the 2-sided 95% CI is greater than 0.67. The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. If the lower limit of the nonparametric CI for the median exceeds 0, the corresponding objective will be considered to have been met. For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.	patients who have effective hemostasis, will be summarized with a 95% CI. ~~The null and alternative hypotheses tested to support this analysis are:~~ ~~H0: $\pi = 0.67$~~ ~~H1: $\pi \neq 0.67$~~ ~~The study will be considered to have met its primary efficacy objective if the proportion of patients with effective hemostasis is statistically significantly higher than 67% ($p < 0.05$) using a 2-sided Chi-Square test with $\alpha = 0.05$, or the lower bound of the 2-sided 95% CI is greater than 0.67.~~ The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. ~~If the lower limit of the nonparametric CI for the median exceeds 0, the corresponding objective will be considered to have been met.~~ For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.		
Synopsis, Statistical Analysis Methods for Safety	Safety will be assessed by examination of 30-day survival status, AEs (including SAEs and TEs), vital signs, clinical laboratory measurements, and antibodies to andexanet, FX, FXa, and HCPs. These data will be descriptively summarized. All potential post-surgical bleeding events and TEs will be confirmed by adjudication.	***All safety analyses will be performed in the Safety Analysis Population***. Safety will be assessed by examination of 30-day survival status, AEs (including SAEs and TEs), vital signs, ***physical examination, centrally adjudicated deaths***, clinical laboratory measurements, and antibodies to andexanet, FX, FXa, and HCPs. These data will be descriptively summarized. All potential post-surgical ***major*** bleeding events and TEs will be confirmed by adjudication.	Revised to include additional safety assessments and clarify that safety analyses will be performed on the Safety Analysis Population.	S

1.4 Summary of Relevant Clinical Experience with Andexanet	Completed trials include a single ascending dose Phase 1 study (Study 11 501) in 32 healthy subjects; a Phase 1 study (Study 14 506) examining the PK and PD of andexanet in 10 young vs. 10 older subjects receiving apixaban; a Phase 1 PK/PD study (Study 16-512) to evaluate the PK, PD, safety, and tolerability of andexanet produced by an updated manufacturing process (Generation 2); a Phase 2 dose-ranging study (Study 12-502) in 152 healthy subjects to determine the appropriate doses to reverse the anticoagulant effects of apixaban, rivaroxaban, enoxaparin and edoxaban; and 2 Phase 3 studies in 148 healthy older subjects (50 75 years) to confirm that the doses defined in the Phase 2 study reverse apixaban (Study 14-503) and rivaroxaban (Study 14-504). Details of the completed studies may be found in the Investigator's Brochure.	Completed trials include a single ascending dose Phase 1 study (Study 11 501) in 32 healthy subjects; a Phase 1 study (Study 14 506) examining the PK and PD of andexanet in 10 young vs. 10 older subjects receiving apixaban; a Phase 1 PK/PD study (Study 16-512) to evaluate the PK, PD, safety, and tolerability of andexanet produced by an updated manufacturing process (Generation 2); a Phase 2 dose-ranging study (Study 12-502) in ~~152~~ ***157*** healthy subjects to determine the appropriate doses to reverse the anticoagulant effects of apixaban, rivaroxaban, enoxaparin and edoxaban; and 2 Phase 3 studies in 148 healthy older subjects (50 75 years) to confirm that the doses defined in the Phase 2 study reverse apixaban (Study 14-503) ~~and~~ ***or*** rivaroxaban (Study 14-504). Details of the completed studies may be found in the Investigator's Brochure.	Edited to update numbers/details.	NS
1.4.1 Phase 1 Study of Andexanet Alone in Healthy Subjects (11-501)	Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in 32 healthy subjects, each of whom received 1 of 4 doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.6.	Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, ***tolerability***, PK, and PD of andexanet in 32 healthy subjects, each of whom received 1 of 4 doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.6.	Edited to align with IB.	NS
Section 1.4.2 Phase 1 Study of Andexanet in Healthy Younger Versus Older Subjects (14-506)	Study 14-506 was a Phase 1 non-randomized, open-label study of andexanet in healthy younger (18 45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin	Study 14-506 was a Phase 1 ~~non-~~randomized, open-label study of andexanet in healthy younger (18 45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban ***for 3 hours and*** then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin	Edited to align with IB and update details.	NS

	generation (TG) in older and younger subjects were similar. The safety data from this study are summarized in Section 1.4.6.	generation (TG) in older and younger subjects were similar. The safety data from this study are summarized in Section 1.4.6.		
1.4.3 Phase 1 PK/PD Study to Evaluate the PK, PD, Safety, and Tolerability of Andexanet Produced by an Updated Manufacturing Process (Generation 2) (16-512-Direct Inhibitors)	Study 16-512-Direct Inhibitors was a randomized, double-blind study in healthy volunteers dosed to steady state with FXa inhibitors, designed to: 1) demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes; 2) evaluate the degree to which Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo; and 3) evaluate the safety and tolerability of Generation 2 andexanet.	Study 16-512-Direct Inhibitors was a randomized, double-blind, ***placebo-controlled*** study in healthy volunteers dosed to steady state with FXa inhibitors, designed to: 1) demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes; 2) evaluate the degree to which Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo; and 3) evaluate the safety and tolerability of Generation 2 andexanet.	Edited to align with IB.	NS
1.4.4 Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects (12-502)	Andexanet exhibited dose-proportional PK for both C_{max} (maximum observed concentration) and AUC (area under the curve) with a mean terminal half-life ($t_{½}$) of approximately 8 hours.	Andexanet exhibited dose-proportional PK for both ~~C_{max}~~ maximum observed concentration (***C_{max}***) and ~~AUC~~ (area under the curve (***AUC***) with a mean terminal half-life ($t_{½}$) of approximately ~~8~~ ***4*** hours.	Edited to align with IB and update number.	NS
1.4.6 Summary of Safety from Clinical Studies of Healthy Subjects	This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred 18 days after dosing. No severe or life-threatening AEs have been reported. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent, and have rarely required treatment (2 subjects received 1 dose each of diphenhydramine). With the exception of 2 subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting. Andexanet was associated with dose-dependent increases in prothrombin fragment 1 and 2 (F1+2), thrombin-	This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred ~~18 days~~ ***approximately 3 weeks*** after dosing. No severe or life-threatening AEs have been reported. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent, and have rarely required treatment (2 subjects received 1 dose each of diphenhydramine). With the exception of 2 subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting. Andexanet was associated with dose-dependent increases in prothrombin fragment 1 and 2 (F1+2), thrombin-antithrombin	Edited to align with IB.	NS

	antithrombin (TAT), and fibrin degradation product (D-dimer), and with a concomitant decrease in tissue factor pathway inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with clinical evidence of thrombosis. Compared with administration of andexanet alone (Study 11 501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of an anticoagulant. In all completed studies to date, among healthy subjects treated with andexanet, 10-12% developed low-titer non-neutralizing antibody (nAb) to andexanet.	(TAT), and fibrin degradation product (D-dimer), and with a concomitant decrease in tissue factor pathway inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with clinical evidence of thrombosis. Compared with administration of andexanet alone (Study 11 501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of an anticoagulant. In all completed studies to date, among healthy subjects treated with andexanet, ~~10-12~~ ***approximately 11%*** developed low-titer non-neutralizing antibody (nAb) to andexanet.		
1.4.7 Phase 3b/4 Study in Patients with Acute Major Bleeding (14-505)	Baseline characteristics included a mean age of 77 years, 47% female, 87% Caucasian, and median body mass index 27 kg/m2. A total of 90 patients (26%) had gastrointestinal or urinary bleeding, 227 patients (64%) had an intracranial hemorrhage, and 35 patients (10%) had other types of bleeding. … Similarly, no clinically significant changes in vital signs and/or physical examination findings have been observed. Finally, no nAbs to FX, FXa, or andexanet have been detected in the study.	Baseline characteristics included a mean age of 77 years, 47% female, 87% Caucasian, and median body mass index 27 kg/m2. A total of 90 patients (26%) had gastrointestinal ~~or urinary~~ bleeding, 227 patients (64%) had an intracranial hemorrhage, and 35 patients (10%) had other types of bleeding. … Similarly, no clinically significant changes in vital signs and/or physical examination findings have been observed. ~~Finally, no nAbs to FX, FXa, or andexanet have been detected in the study~~ ***Twenty patients (5.7%) had confirmed positive results for anti-andexanet antibodies after treatment. The titers were nearly all low values with no neutralizing activity in any patient samples.***	Edited to align with IB and updated details.	NS
2.4 Safety Objectives	To evaluate the overall safety of andexanet.	• To evaluate the overall safety of andexanet, ***including AEs, SAEs, vital signs, physical examinations, clinical laboratory measurements, thrombotic events (TEs),***	Added text to clarify which safety parameters will	NS

		mortality, and immunogenicity.	be measured.	
3.1 Overall Study Design and Plan: Description	The bolus will begin prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision; designated as Time 0). It is possible that the bolus or continuous infusion may be ongoing at the start of surgery. Additional andexanet, be it for extended treatment or re-dosing, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-operative complications are met (see Section 6.2). … Prior to surgery, the American Society of Anesthesiologists classification for each patient will be recorded.	The bolus ~~will begin~~ ***must be completed immediately*** prior to~~,~~ ~~but not more than 30 minutes before,~~ the start of surgery (i.e., at the first incision; designated as Time 0). ~~It is possible that the bolus or continuous~~ ***The*** infusion ~~may be ongoing at~~ ***should continue from prior to*** the start of surgery~~.~~ ***(initial skin incision) until the end of surgery (close of skin incision). If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes).*** Additional andexanet, be it for extended treatment or re-dosing, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-~~operative~~ ***postoperative*** complications are met (see Section 6.2). … ~~Prior to surgery, the American Society of Anesthesiologists classification for each patient will be recorded.~~	Removed sentence because this point is addressed elsewhere in the protocol.	NS
3.4.1 Study Population	The study will enroll patients between the ages of 18 and 85 who have recently taken an FXa inhibitor (i.e., within 15 hours prior to surgery or if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin]) and who require urgent surgery for which reversal of anti-fXa activity is judged necessary. Only patients who are in need of surgery that, in the opinion of the Investigator, cannot be delayed by 12 hours are to be enrolled. Procedures that are associated with a low bleeding risk are not eligible.	The study will enroll patients between the ages of 18 and 85 ***years*** who have recently taken an FXa inhibitor ~~(i.e.,~~ within 15 hours prior to ***start of*** surgery ~~or if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin])~~ and who require urgent surgery for which reversal of anti-fXa activity is judged necessary. ~~Only patients~~ ***If the time from last dose is unknown or greater than 15 hours, the patient may be enrolled provided a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin]). In such cases the start of surgery must be no greater than 4***	Language added to more accurately detail potential risks.	S

		hours after the blood collection time for the local test. ***Patients*** who are in need of ~~surgery that, in the opinion of the Investigator, cannot be delayed by~~ ***urgent surgery within*** 12 hours ~~are to be enrolled. Procedures that are associated with a low~~ ***of consent may be enrolled. Patients undergoing procedures for which the risk of clinically meaningful uncontrolled or unmanageable*** bleeding ~~risk~~ ***is low*** are not eligible. ***Patients with life-threatening bleeding (International Society on Thrombosis and Haemostasis [ISTH] definition, see Section 4.2) are also not eligible.*** ***It is expected that eligible procedures may have varying degrees of tissue trauma but still have clinically relevant bleeding risk for which the reversal of FXa inhibition is judged necessary. For example, surgeries in a confined space (e.g., spinal cord decompression) can be considered to be at high bleeding risk even with relatively little tissue trauma, as opposed to an intra-abdominal surgery. Anticipated surgery types may include, but are not limited to, abdominal, thoracic, orthopedic, gynecological open and laparoscopic surgery. To ensure an adequate number of patients with certain key surgery types, abdominal surgeries (including both open and laparoscopic) and orthopedic surgeries will each comprise approximately 20% of the enrolled population. Patients undergoing only non-surgical invasive procedures (e.g. skin biopsies, lumbar puncture, cardiac catheterization, ERCP) will be excluded.*** ***To align with previous studies of andexanet [7], the Efficacy Analysis Population for the study will only include patients whose***		

		central laboratory-determined anti-fXa activity is ≥ 75 ng/mL (≥ 0.25 IU/mL for patients receiving enoxaparin).		
3.4.2 Rationale for the Dose Regimen	• Low dose: 400 mg IV bolus at a rate of 30 mg/min (duration of approximately 15 minutes) followed by a continuous infusion at a target rate of 4 mg/min for 120 minutes irrespective of the duration of surgery (extended infusion at the discretion of the Investigator). • High dose: 800 mg IV bolus at a rate of 30 mg/min (up to 30 minutes) followed by a continuous infusion at a target rate of 8 mg/min for 120 minutes irrespective of the duration of surgery (extended infusion at the discretion of the Investigator). Data from the Phase 3 studies with apixaban and rivaroxaban, as well as a recently completed Phase 1 study of Generation 2 andexanet in healthy volunteers (Study 16-512-Direct Inhibitors; Section 1.4.3), confirm the levels of FXa inhibition and recovery of TG observed in the Phase 2 study.	• Low dose: 400 mg IV bolus at a rate of 30 mg/min (duration of approximately 15 minutes) followed by a continuous infusion at a target rate of 4 mg/min for 120 minutes irrespective of the duration of surgery ~~(extended infusion at the discretion of the Investigator)~~. • High dose: 800 mg IV bolus at a rate of 30 mg/min (~~up to~~ ***duration of approximately*** 30 minutes) followed by a continuous infusion at a target rate of 8 mg/min for 120 minutes irrespective of the duration of surgery (~~extended infusion at the discretion of the Investigator~~). ***Extended infusion at the low-dose (4 mg/min) may be administered for up to an additional 4 hours after initial dosing (bolus + infusion) is completed (1) in order to ensure mandatory continuous infusion from start to end of surgery, and (2) may continue into the immediate post-operative coverage per investigator discretion. Total dosing time (initial bolus + 120 minute infusion + any extended infusion) should be less than 6.5 hours.*** ***Evidence to support this dosing regimen comes from PK/PD modeling that included results from the ANNEXA-4 study in bleeding patients.*** Data from the Phase 3 studies with apixaban and rivaroxaban, as well as a recently completed Phase 1 study of Generation 2 andexanet in healthy volunteers (Study 16-512-Direct Inhibitors; Section 1.4.3), confirm the levels of FXa inhibition and recovery of TG observed in the Phase 2	Included more details about dosing.	NS

		study.		
3.4.3 Rationale for Extended Infusion or Re-Dosing of Andexanet	N/A … Investigators will be required to document in the case report form (CRF) the clinical justification for why subjects require extended infusion of andexanet or additional dosing of andexanet during surgery.	***Re-dosing Criteria:*** ***Factors that may determine if re-dosing is appropriate include the treating surgeon's consideration of patient factors, such as degree of visible bleeding, hemodynamic stability, need for hemostatic support products, or to avoid reoperation to control bleeding. The Investigator may also consider clinical suspicion that the patient has levels of FXa inhibition sufficient to contribute to bleeding based on patient factors such as time from last FXa inhibitor dose, safety assessments required by the protocol or routine care and renal function. Additionally, the need for re-operation to control bleeding may be considered reason re-dose to avoid the additional procedure.*** … Investigators will be required to document in the ***electronic*** case report form (***e***CRF) the clinical justification for why subjects require extended infusion of andexanet or additional dosing of andexanet during surgery.	Added a small section to define criteria for re-dosing.	S
3.5 Safety Plan and Monitoring	To mitigate the risk of TEs, Investigators are encouraged to consider resumption of an anti-thrombotic agent as soon as it is clinically appropriate. … Whether or not patients have been discharged from the hospital, they will undergo the Study Day 3, and Follow-up Day 30 visits to assess safety	To mitigate the risk of TEs, Investigators are encouraged to consider resumption of an anti-thrombotic agent ***(preferably oral)*** as soon as it is clinically appropriate. ***Additional clinical precautions to mitigate thrombotic risk in postoperative care such as early mobilization, sequential compression devices or other routine measures should also be strongly considered.*** … Whether or not patients have been discharged from the hospital, they will undergo the ***Study Day 2***, Study Day 3, and Follow-up Day 30 visits to assess safety.	Added details on precautions.	NS

3.6 Benefit and Risk Assessment	Factor Xa inhibitors are a significant therapeutic advance in several indications. However, a significant risk of anticoagulation with FXa inhibitors is the potential for uncontrolled bleeding. While andexanet is approved for the management of acute major bleeding related to FXa inhibitor use, it is unknown whether it is efficacious and safe in patients who require urgent surgery in the setting of recent use of an FXa inhibitor. Andexanet may be beneficial in reversing anticoagulation and, thus, facilitating normal hemostasis during the surgical procedure.	Factor Xa inhibitors are a significant therapeutic advance in several indications. However, a significant risk of anticoagulation with FXa inhibitors is the potential for uncontrolled bleeding. ***In the case of urgent surgery, a delay in surgical treatment necessary to sufficiently diminish anti-coagulant concentrations could potentially result in deleterious clinical consequences***. While andexanet is approved for the management of acute major bleeding related to FXa inhibitor use, it is unknown whether it is efficacious and safe in patients who require urgent surgery in the setting of recent use of an FXa inhibitor. Andexanet may be beneficial in reversing anticoagulation ***due to FXa inhibition*** and, thus, facilitating normal hemostasis during the surgical procedure. … ***Procedural risks inherent to the urgent surgical procedure itself would vary from based on the procedure type and individual patient risk factors, and should be additionally communicated to the patient by the treating physician.***	Added details to mitigate risks to patients.	NS
4.3 Criteria for Discontinuation from the Study	The informed consent process will clearly alert patients to the negative effect that failure to complete the study has on its credibility. … Reasons for all study withdrawals will be recorded.	~~The informed consent process will clearly alert patients to the negative effect that failure to complete the study has on its credibility.~~ … Reasons for all study withdrawals will be recorded ***in the eCRF***.	Removed text to clarify the informed consent process.	NS
4.4 Criteria for Discontinuation of Andexanet	Patients who discontinue study drug may still continue in the study. Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, in which case they should undergo an Early Termination	Patients who discontinue study drug may still continue in the study. Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, in which case they should undergo an Early Termination	Added text to clarify follow-up safety procedures for certain patients.	NS

	visit. … Reasons for all discontinuations will be recorded.	visit~~.~~ ***(complete the same procedures as Day 30 Visit).*** … Reasons for all discontinuations will be recorded ***in the eCRF***.		
5.0	A summary of the patient visits and clinical evaluations can be found in Appendix A. Details on efficacy and safety assessments can be found in Section 10.0. Laboratory assessments or procedures performed per standard of care at presentation, but before signing of informed consent, may be used to assess eligibility.	A summary of the patient visits and clinical evaluations can be found in Appendix A. Details on efficacy and safety assessments can be found in Section 10.0. Laboratory assessments***, clinical assessments, and/***or procedures performed per ***investigator or institutional*** standard of care at presentation, but before signing of informed consent, may be used to ~~assess eligibility~~ ***fulfill protocol requirements***.	Language changed to be inclusive of all assessments/ procedures and to provide clarity.	NS
5.1 Screening Period ~~5.1.1 Subject Identification Numbers~~	Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have met the inclusion and exclusion criteria.	~~Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have met the inclusion and exclusion criteria.~~ ***Patients will be identified by their need for urgent surgery that cannot be delayed and time from last dose of an FXa inhibitor. Informed consent will be administered followed by assignment of a patient identification number. Eligibility will be assessed by completion of demographics, medical history, physical examination, determination of last time of anticoagulated dose or plasma level. Baseline safety assessment will be performed inclusive of vital signs and weight, collection of local clinical laboratory results. Baseline efficacy and safety labs will be collected for analysis by a central laboratory. Following execution of the informed consent, changes***	Language added to clarify how patients are identified and the assessments performed during Screening.	NS

		in patient status that meet the definition of AEs will be recorded (Section 9.0).		
5.2 Visit Procedures (Days 1 ~~to 30 37~~***, 2, 3, and 30***)	The visit procedures are described in the Schedule of Activities (Appendix A).	~~The visit procedures are described in the Schedule of Activities (Appendix A).~~ ***Day 1 Inpatient*** ***On Day 1, patients will receive treatment with andexanet and will undergo the urgent surgery. Prior to start of dosing, patients will have the general health status assessed and categorized according to the American Society of Anesthesiologists Classification, repeat safety assessments (serial vital signs, repeat physical examination, and local labs). Study specific assessments and central laboratory samples will be collected to assess in vitro hemostasis.*** ***The dose of andexanet will be selected based on anticoagulant product/brand, dose, and time of last dose of anticoagulant the patient is taking. The duration of the surgery will determine the total dose and duration of andexanet administered. Generally, it is planned for patients to complete the bolus and start infusion immediately prior to start of surgery and receive andexanet infusion, including extended dosing as necessary, for the duration of their surgical procedure. During the surgery, the investigator and staff will provide assessment of hemostasis and record all supporting medications related to hemostasis support. Patients should remain hospitalized on Day 1. The patient will be scheduled for study Day 2 visit.*** ***Day 2 and Day 3*** ***Follow-up visits on Days 2 and 3 will be conducted as an inpatient or outpatient. Patients will receive safety assessments (vital signs, physical examination, and local***	Details of procedures performed on specific days as well as rationale for dose selection have been added to the text to provide clarity.	S

		laboratory testing) along with collection of samples for central laboratory analysis to assess hemostasis. Diagnostic and therapeutic products supporting hemostasis will be assessed, documented and reported. Adverse events and concomitant medications will be recorded. The patient-will be scheduled for study Day 30 visit. ***Day 30*** ***The Follow-up visit on Day 30 will be conducted as an inpatient or outpatient. Safety assessments will be performed (vital signs, physical examination, weight, and local laboratory testing) along with collection of samples for central laboratory analysis to assess hemostasis. Adverse events and concomitant medications will be recorded. The investigator will assess and report duration of hospitalization by unit type (emergency, critical care units, post-op units, etc.) and document the survival status of the patient.*** ***Procedures performed at the Day 30 visit will also be performed for all early terminating patients (Section 5.4).***		
5.3	During the study, additional clinical visits may be scheduled at the Investigator's discretion in order to follow or evaluate AEs. The reason for an unscheduled visit will be recorded. The following must be performed at an unscheduled visit: • Record the reason for the unscheduled visit. • Record AEs since last study visit. • Record use of concomitant medication since last study visit.	During the study, additional clinical visits may be scheduled at the Investigator's discretion in order to ~~follow or evaluate AEs.~~ ***care for the patient***. The reason for an unscheduled visit will be recorded ***in the eCRF***. The following must be performed at an unscheduled visit: • Record the reason for the unscheduled visit. • Record AEs since last study visit. • Record use of concomitant medication since last study visit.	Wording changed for clarity and specified additional information to be captured at unscheduled visits.	NS

	Additional procedures may be performed at an unscheduled visit as deemed necessary by the Investigator. These may include any of the central or local laboratory testing done at scheduled visits, vital signs, additional evaluations for bleeding, or assessment of AEs.	Additional procedures may be performed at an unscheduled visit as deemed necessary by the Investigator. These may include any of the central or local laboratory testing done at scheduled visits, vital signs, additional evaluations for bleeding, or assessment of AEs. ***Record study specified procedures and data captured as unscheduled visits.***		
5.4	An Early Termination visit will be conducted if the patient discontinues from the study before the Follow-up Day 30 visit. Procedures at this visit will include the following: • Record the reason for early termination. • Record AEs since last study visit. • Record use of concomitant medication since last study visit. • Record dates of use of anticoagulant(s) on the anticoagulant CRF. • Perform a final assessment of bleeding. • Collect central laboratory specimens for TG and antibodies (anti andexanet, anti-fX, anti fXa, anti-HCP, and nAbs). Vital signs and local laboratory assessments for complete blood count (CBC) and chemistry should also be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.	An Early Termination visit will be conducted if the patient discontinues from the study before the Follow-up Day 30 visit. ~~Procedures at this visit will include the following~~ ***In addition to the Day 30 procedures outline in Section 5.2, the following procedures will be performed at the ET visit***: • Record the reason for early termination. • Record AEs since last study visit. • Record use of concomitant medication since last study visit. • Record dates of use of anticoagulant(s) on the anticoagulant ***e***CRF. • Perform a final assessment of bleeding. • Collect central laboratory specimens for TG and antibodies (anti andexanet, anti-fX, anti fXa, anti-HCP, and nAbs). Vital signs and local laboratory assessments for complete blood count (CBC) ~~and chemistry~~ should also be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.	Clarified that the anticoagulant CRF is an electronic CRF. Removed chemistry laboratory assessments from required assessments at Early Termination visit.	NS
6.2 Dosing and Administration	The initial andexanet dosing regimen will consist of an IV bolus, immediately followed by an IV continuous infusion lasting for 2 hours, irrespective of the	***The timing of andexanet dosing in relation to the surgical procedure is depicted schematically in Figure 3.***	Revised text to more clearly and accurately explain	S

	duration of surgery. The start of the bolus will occur prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision). It is possible that the bolus or infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens (Table 2). If the initial andexanet dosing regimen (bolus plus continuous infusion; ~2.5 hours) is completed prior to the end of the procedure, the infusion should continue at a low dose (4 mg/min) through the end of the surgery and the immediate post-operative period. To facilitate the extended infusion, approximately 30 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation. The total length of the initial course of andexanet (initial bolus/infusion plus extended infusion) should last no longer than 6 hours. If a post-operative patient meets the applicable criteria for andexanet re-dosing (Table 2), he/she may be re-dosed. All patients that are re-dosed will be administered a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes). If a patient is re-dosed, a baseline anti-fXa activity sample will be drawn beforehand; no post-initiation anti-fXa activity will be obtained.	***<Figure 3 inserted>*** ***Key Dosing Directives:*** • ***Initial Bolus (low/high-dose) must be completed prior to start of surgery (initial skin incision)*** • ***Initial dosing (low/high-dose bolus + 120-min infusion) should be completely administered irrespective of surgery length.*** • ***Infusion should continue throughout the duration of surgery, defined as skin incision to skin closure.*** • ***Extended infusion (up to 4 hours at 4 mg/min) (1) may be administered to ensure continuous infusion to match the duration of the surgery, and (2) can additionally proceed into the immediate postoperative period per investigator discretion.*** ***Initial Dosing (Bolus + 2-hour infusion):*** The initial andexanet dosing regimen will consist of ***the following:*** ***1.*** an IV bolus, ***(to be completed prior to surgery)*** ***followed*** immediately ~~followed~~ by ***2.*** an IV continuous infusion lasting for ***at least*** 2 hours, ***(***irrespective of the duration of surgery***).*** The ~~start of the~~ bolus ~~will occur prior to, but~~ ***should be initiated*** not more than 30 minutes before, ***and must be completed by,*** the start of surgery (i.e., at the first incision). ***The bolus will be followed immediately by a continuous infusion lasting at least 120 minutes, irrespective of the length of the surgery.*** It is possible that the ~~bolus or~~ infusion may be	andexanet dosing rules in relation to surgery timing and procedures.	

		ongoing at the start of surgery. There are 2 possible dosing regimens (Table 2). ***If the end of surgery occurs prior to completion of the initial 2-hour infusion, the infusion should continue into the postoperative period until it is completed (120 minutes).*** ***Extended Infusion (maximum of 4 additional hours at 4 mg/min)*** ***Extended Infusion may be administered after completion of initial dose (bolus + 2-hour infusion):*** ***1. To ensure continuous intraoperative infusion lasts the duration of the surgery, (if initial 2 hour infusion is completed prior to end of surgery)*** ***and*** ***2. To provide coverage during the immediate postoperative period, per investigator clinical judgement*** If the initial andexanet dosing regimen (bolus plus ~~continuous~~ ***2-hour*** infusion~~; ~ 2.5 hours~~) is completed prior to the end of the procedure, the infusion should continue at a low dose (***only*** 4 mg/min) ***at least*** through the end of the surgery ~~and~~ ***(skin closure).*** ***Extended infusion may also continue after the end of surgery per investigator clinical judgement if deemed appropriate for*** the immediate post-operative period. To facilitate the extended infusion, approximately 30***-45*** minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation. ~~The total length of the initial course of andexanet (initial~~		

		~~bolus/infusion plus extended infusion) should last no longer than 6 hours.~~ ***Allowable Total Length of Dosing (Initial + Extended = up to 6.5 hours):*** ***The total length of the initial dosing duration of andexanet (initial infusion plus extended infusion) should last no longer than 6.5 hours. Total study drug administration greater than 6.5 hours, while not prohibited, is strongly discouraged.*** ***Re-dosing:*** If a post-operative patient meets the applicable criteria for andexanet re-dosing (Table 2), he/she may be re-dosed. All patients that are re-dosed will be administered a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes). If a patient is re-dosed, a baseline anti-fXa activity sample will be drawn beforehand ***for central laboratory analysis;*** no post-initiation anti-fXa activity will be ~~obtained~~ ***analyzed via local laboratory.***		
7.2.2 Blood Products	Use of procoagulant factor infusions (e.g., 3 or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) and whole blood intraoperatively or within 12 hours following surgery will result in the patient being considered having poor hemostatic efficacy (see Table 3) with andexanet.	Use of procoagulant factor infusions (e.g., 3 or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) and whole blood intraoperatively ~~or within 12 hours following surgery~~ will result in the patient being considered having poor hemostatic efficacy (see Table 3) with andexanet.	Removed text to clarify the criteria for poor hemostatic efficacy.	NS
7.3 ***Post-Surgical Bleeding and*** Rescue Therapy	In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated for patients, due to post-surgical bleeding events. Investigators will therefore be allowed to deliver a second dose of andexanet as rescue therapy should such a situation arise. If rescue re dosing is deemed necessary, Investigators will be required to document in the CRF the clinical justification for why	In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated ~~for patients~~***during surgery***, due to post-surgical bleeding events. Investigators will therefore be allowed to deliver a second dose of andexanet ***(low-dose bolus + 120 minute infusion only)*** as rescue therapy should such a situation arise. If rescue re dosing is deemed necessary,	Added text to clarify when and how a second dose of andexanet shall be delivered, and to further clarify the criteria for poor hemostatic	NS

	subjects require additional dosing of andexanet. Re dosing procedures will mirror those required for the initial andexanet dosing. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for re-dosing are outlined in Section 6.2.	Investigators will be required to document in the ~~CRF~~***eCRF*** the clinical justification for why subjects require additional dosing of andexanet. ~~Re dosing~~***Study*** procedures will mirror those required for the initial andexanet dosing. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for re-dosing are outlined in Section 6.2. ***If a patient is confirmed to have post-surgical bleeding by the EAC, then they will be considered to have poor hemostatic efficacy (irrespective of the treatment given for bleeding, if any).***	efficacy.	
10	N/A	***Assessments, testing and treatment schedules are detailed in Appendix A. No reference to timing or frequency is described below.***	Language added for clarity.	NS
10.1 Baseline Assessments	N/A	***Baseline Assessments***	Section added to provide information on assessments performed at Baseline	S
10.1.1 ~~Efficacy Assessments~~ ***Informed Consent***	~~Efficacy assessments that require collection and evaluation of laboratory samples are described in the subsections that follow; other efficacy assessments are described in Section 11.5.2.~~	***An IRB/EC approved informed consent will be administered prior to performing study specific procedures or assessments. Administering informed consent is a process and will be documented in source documents. The current IRB/EC version of the consent will be used.***	Section titled "Efficacy Assessments" removed and assessments previously contained in this section were moved to a new "Central Laboratory Testing" section (see below). New	S

			information added to the updated section heading to specify when/how informed consent is obtained.	
10.1.2 Demographics	N/A	***Demographics will record the age, sex, race and ethnicity of patients. Race will be recorded (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific, White), and ethnicity will be recorded as Hispanic or Latino or Non-Hispanic or Latino.***	Section added to specify what demographic characteristics will be captured at Baseline.	S
10.1.3 Medical History	N/A	***Patients will have a detailed medical history completed as part of baseline assessments. Diagnosis, year of onset and status will be reported. Status will consist of an end date or documentation as ongoing for the condition. Diagnosis should be documented and not signs and symptoms. Events with current treatment will have the treatment recorded in concomitant medications and therapies.***	Section added to specify what medical history will be captured at Baseline.	S
10.1.4 Prior and Concomitant Medications	N/A	***Patients will be asked about their current physician prescribed medications, over the counter medications and any herbal or nutritional supplements. The generic name is preferred for Electronic Data Capture (EDC) entry. The dose, posology, frequency, start and stop dates and the diagnosis for use will be recorded.***	Section added to specify what information regarding prior and concomitant medications should be collected at Baseline.	S
10.1.5 Anticoagulant Dose or Plasma Level	N/A	***Patients will be asked about the brand, dose and time of last dose of their anticoagulant. For patients who received the last dose of***	Section added to specify what information	S

		FXa inhibitor more than 15 hours (or an unknown time) prior to start of surgery, a local anti-fXa activity level may be obtained to allow enrollment of patients with >100 ng/mL levels. See Section 10.2.1 below on details for this local testing.	regarding anticoagulant use should be collected at Baseline and when anti-fXa activity levels may be used for enrollment.	
10.1.6 American Society of Anesthesiologists Physical Status Classification (ASA PS)	N/A	***The American Society of Anesthesiologist Physical Status Classification is used to evaluate and describe the general health of patients prior to use of anesthetics or prior to surgery. The ASA PS consists of 6 categories to describe a patient's physical status (Appendix F). It will be used to describe the population enrolled in the trial. It is not an assessment of operative risk, and will not be repeated during the study.***	Section added to describe ASA PS assessment performed at Baseline.	S
10.1.7 Eligibility Assessment	N/A	***Following completion of assessments and screening testing, the investigator will determine eligibility of the patient by comparing results to inclusion and exclusion criteria. Note: it is Portola Pharmaceuticals Policy not to grant exceptions or waivers for inclusion and exclusion criteria.***	Section added to clarify how eligibility will be assessed.	S
10.1.8 Patient Identification Numbers	N/A	***Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have signed informed consent and met the inclusion and exclusion criteria.***	Section added to specify how and when patient identification numbers are assigned.	S
10.2 Central Laboratory Testing	N/A	***Central Laboratory Testing***	Section heading has been changed to reflect assessments performed at	S

			the central laboratory (anti-fXa activity, thrombin generation, TFPI, Anti-IIa activity, and antibody testing).	
~~10.1.1.~~ ***10.2.1*** Anti-fXa Activity	Anti-fXa activity will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Anti-fXa activity will be measured by a modified chromogenic assay. These assays will be performed at a Central Laboratory.	Anti-fXa activity will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Anti-fXa activity will be measured by a modified chromogenic assay. These assays will be performed at a Central Laboratory. ***Local laboratory anti-fXa activity testing may be utilized additionally by sites to ascertain eligibility (>100 ng/ml) if the time of last dose of FXa inhibitor is greater than 15 hours (or unknown), provided the time is known. Local laboratory testing post-andexanet administration should be done with caution due to potential invalidity of local lab results from excessive sample dilution.***	Language added to reflect that local laboratory anti-fXa activity testing may be used to determine eligibility in patients whose last dose of fXa inhibitor was >15 hours.	S
~~10.1.2~~ ***10.2.2*** Thrombin Generation	10.1.2 Thrombin Generation	~~10.1.2~~ ***10.2.2*** Thrombin Generation	Subheading numbering changed based on change to Section 10.2 heading (see above)	NS
~~10.1.3~~ ***10.2.3*** Tissue Factor Pathway Inhibitor	10.1.3 Tissue Factor Pathway Inhibitor	~~10.1.3~~ ***10.2.3*** Tissue Factor Pathway Inhibitor	Subheading numbering changed based on change to Section 10.2 heading (see	NS

			above)	
~~10.1.4~~ ***10.2.4*** Anti-IIa Activity	10.1.4 Anti-IIa Activity	~~10.1.4~~ ***10.2.4*** Anti-IIa Activity	Subheading numbering changed based on change to Section 10.2 heading (see above)	NS
~~10.1.5.3~~ ***10.2.5*** Antibody Testing	Determination of the possible presence of antibodies to FX (human) and FXa (human) will be done at specific time points (see Appendix A) using the modified Bethesda assay. Antibodies against andexanet and HCPs will assessed using standard immunogenicity assays. For any sample that is positive for antibodies against andexanet, the potential for nAb activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a Central Laboratory.	Determination of the possible presence of antibodies to FX (human) and FXa (human) will be done at specific time points (see Appendix A) using the modified Bethesda assay. Antibodies against andexanet and HCPs will ***be*** assessed using standard immunogenicity assays. For any sample that is positive for antibodies against andexanet, the potential for nAb activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a Central Laboratory.	This section has been moved from "Safety Assessments" to "Central Laboratory Testing" and the subsection numbering changed accordingly. A grammatical error has been corrected.	NS
~~10.1.5~~ ***10.3*** Safety Assessments (Other than Adverse Events)	10.1.5-Safety Assessments (Other than Adverse Events)	~~10.1.5~~ ***10.3*** Safety Assessments (Other than Adverse Events)	Section numbering changed.	NS
~~10.1.5.1~~ ***10.3.1*** Vital Signs	Vital signs include temperature, systolic blood pressure (SBP), diastolic blood pressure, heart rate, and respiratory rate.	Vital signs include temperature ***(˚C)***, systolic blood pressure (SBP) ***(mmHg)***, diastolic blood pressure ***(mmHg)***, heart rate ***(beats per minute)***, and respiratory rate ***(respirations per minute)***.	Section numbering changed and units added to vital sign assessments.	NS
~~10.1.5.2~~ ***10.3.2*** Physical Examination	A focused physical examination will be performed on all patients at various time points (see Appendix A) before and after the surgical procedure. The examination will include, at a minimum, any component relevant to the indication for surgery (e.g., abdominal examination for appendicitis, hip	A ~~focused~~ physical examination will be performed on all patients at various time points ~~(see Appendix A)~~ before and after the surgical procedure. The examination will include, at a minimum, any component relevant to the indication for surgery (e.g., abdominal examination for appendicitis, hip	Language changed to allow for broad physical examination.	NS

	examination for hip fracture, neurologic examination for spinal cord compression) and an assessment of the surgical incision site (post-operative only).	examination for hip fracture, neurologic examination for spinal cord compression) and an assessment of the surgical incision site (post-operative only).		
10.3.3 Weight	N/A	***Patient weight will be recorded in kg according to the schedule of assessments in Appendix A.***	Section added to include weight under safety assessments.	NS
~~10.1.5.4~~ ***10.3.4*** Clinical Laboratory Testing	Blood specimens for routine chemistry and hematology will be obtained at selected time points (see Appendix A). The following assays will be performed at the Local Laboratory: • Hematology: hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, WBC differential • Coagulation: INR • Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin • Serum or urine pregnancy test (in women of child bearing potential; see Appendix D)	Blood specimens for routine chemistry and hematology will be obtained at selected time points (see Appendix A). The following assays will be performed at the Local Laboratory: • Hematology: hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, WBC differential • Coagulation: ~~INR~~ ***prothrombin time reported as the INR*** • Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin • Serum or urine pregnancy test (in women of child bearing potential; see Appendix D)	Language changed for clarity.	NS
~~10.1.5.5~~ ***10.3.5*** Optional Local Laboratory Testing of Anti-fXa Levels	Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion criterion 4. Further details and guidance on the conduct of local point-of-care anti-fXa assays can be found in the Laboratory Manual for ANNEXA-S. Investigators are discouraged from evaluating anti fXa activity with local assays after the administration of andexanet, due to the known inaccuracy of post-andexanet results caused by the large	Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion ~~criterion 4.~~criteria. Further details and guidance on the conduct of local ~~point-of-care~~ ***laboratory*** anti-fXa assays can be found in the Laboratory Manual for ANNEXA-S. Investigators are discouraged from evaluating anti fXa activity with local assays after the administration of andexanet, due to the known inaccuracy of post-andexanet results caused by the large sample dilutions	Language changed for clarity.	NS

	sample dilutions associated with commercial anti fXa assays; however, if such testing is deemed necessary, it is strongly recommended that the procedures outlined in the Laboratory Manual be followed.	associated with ***unmodified*** commercial anti fXa assays; however, if such testing is deemed necessary, it is strongly recommended that the procedures outlined in the Laboratory Manual be followed.		
10.4 Intraoperative and Hospitalization Assessments	N/A	***10.4 Intraoperative and Hospitalization Assessments***	Section has been added to describe the assessments to be performed during and following surgery.	S
10.4.1 Surgical Intervention	N/A	***All patients entering the trial are required to have an urgent need for surgical intervention. Institutional or procedural consents should be administered for the surgical intervention in accordance with local requirements and in addition to the study specific informed consent.*** • ***The start of surgery is the initial incision.*** • ***The end of surgery is final skin closure.***	Section has been added to provide details on requirements for surgical intervention and definitions during surgical intervention.	S
10.4.2 Intraoperative Blood Loss	N/A	***Investigators will report blood loss during surgery for each patient. Blood loss will be reported as an estimate of blood loss in milliliters. Blood loss will be reported at the end of surgery. It is an intraoperative assessment and will not be updated for post-closure blood loss.***	Section has been added to describe procedures for reporting blood loss during surgical procedures.	S
10.4.3 Assessment of Intraoperative Hemostasis	N/A	***Intraoperative hemostasis will be captured as an investigator assessment. Categories for assessment are provide in Table 3 (Section 11.5.1).***	Section has been added to define and to describe procedures for reporting intraoperative	S

			hemostasis.	
10.4.4 Blood Products and Hemostatic Treatments	N/A	***Blood products and hemostatic treatments employed as treatment prior to, during and postoperatively will be recorded. The product (generic), dose, route of administration, date and time of use will be recorded along with the reason for use.***	Section has been provided to provide procedures for reporting the use of blood products and other hemostatic treatments before, during, and after surgical procedures.	S
10.4.5 Bleeding-related Diagnostic and Therapeutic Procedures	N/A	***Any diagnostic and/or therapeutic procedures employed prior to, during and postoperatively will be recorded. For diagnostic procedures, the procedure, date, time, results and relevant units or description of results will be captured. Therapeutic procedures will be captured and concomitant medications/treatments with date, time, and posology (if applicable).*** ***As a concomitant treatment, Investigators will record the product (generic name), date, time, indication and posology of colloid or crystalloid treatments used to support hemodynamic status.***	Section has been added to provide procedures for reporting diagnostic and/or therapeutic procedures before, during, and after surgical procedures.	S
10.4.6 Record Hours in Hospital Care Units	N/A	***Investigators will record the date and time of entry into each care unit of the hospital. The date and time of entry and exit for each unit will be reported. This will be locally variable, but categories should be reconciled to the standards below:*** • ***Emergency Department (ED): a unit dedicated to medical and surgical patients in need of immediate care.***	Section has been added to provide procedures for reporting the duration of time spent in hospital care units.	S

		• ***Intensive Care/Critical Care Department (ICU): a specialty medical unit for patients that are seriously ill are maintained under constant medical observation.*** • ***Operating Room (OR): the room where the surgical procedure actually takes place.*** • ***Post-anesthesia Care Unit (PACU): a specialty unit for providing post-anesthesia care for patients recovering from anesthesia.*** • ***General Hospital Department or General Surgical Department: Covers a wide range of types of surgery and procedures on patients.***		
10.5 End of Study Assessments	N/A	***Patients will have their survival status reported on the Day 30 or End of Study visit. This assessment will record the patient's status as alive or provide the date, time and cause of death. Note: see Section 9.0 for AEs reported for all deaths.***	Section has been added to provide details on assessments performed at the end of the study.	S
11.3.3 Efficacy Analysis Population	The efficacy analysis population will include all enrolled patients who receive any amount of andexanet treatment and undergo surgery.	The efficacy analysis population will include all enrolled patients who receive any amount of andexanet treatment ~~and undergo surgery.~~, ***undergo surgery, and have a baseline anti-fXa activity analyzed by central laboratory at or above the evaluability threshold (75 ng/mL for apixaban, edoxaban and rivaroxaban, and 0.25 IU/mL for enoxaparin).***	Added text to clarify inclusion criteria for the efficacy analysis population.	NS
11.5.2.1 Primary Efficacy Endpoint	The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the surgeon's assessment of intra-operative hemostasis and confirmed by adjudication by an independent EAC. For each patient, hemostasis will be judged	The primary efficacy endpoint is the achievement of ~~hemostatic efficacy~~***effective hemostasis***, as determined by the surgeon's assessment of ~~intra-operative~~***intraoperative*** hemostasis and confirmed by adjudication by an independent EAC ***(see Table 3).***	Language changed to add clarity.	NS

	effective if effective hemostasis category is Excellent or Good, and ineffective if effective hemostasis category is Moderate or Poor.	For each patient, hemostasis will be ~~judged~~***considered to be*** effective if ~~effective~~***the intraoperative*** hemostasis category is Excellent or Good, and ineffective if ~~effective~~***the intraoperative*** hemostasis category is Moderate or Poor.		
11.7.1 Adverse Events	All potential post-surgical bleeding events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event.	All potential post-surgical bleeding events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event. ***Postoperative major bleeding events will be additionally adjudicated by the EAC.***	Added language to clarify additional adverse events.	NS
11.7.4 Laboratory Parameters	Clinical laboratory parameters performed at the Central Laboratory (e.g., anti-fXa activity and TG) will be summarized by time point. For patients with anti-fXa activity levels obtained locally by a point-of-care assay, values will be documented but not formally analyzed.	Clinical laboratory parameters performed at the Central Laboratory (e.g., anti-fXa activity and TG) will be summarized by time point. For patients with anti-fXa activity levels obtained ~~locally by a point-of-care~~ ***by a local laboratory*** assay, ***for purposes of eligibility (for patients with a time from last dose greater than 15 hours),*** values will be documented but not formally analyzed.	Specifying the reason for collecting but not formally analyzing certain fXa activity levels.	NS
11.8 Interim Analyses	There is 1 formal interim analysis planned for this study when 50 patients complete the study. This analysis is planned to support the submission for accelerated approval. No adjustment to the type I error rate or CI coverage will be made to account for the interim analysis. Following the formal interim analysis, interim summaries of safety data will be performed periodically at a minimum frequency of every 6 months in order to report safety data from the ongoing study. The DSMB will meet regularly to review the accumulating safety data.	~~There is 1 formal~~ ***During the conduct of the study,*** interim ~~analysis planned for this study when~~***monitoring of safety data by the DSMB will commence after*** 50 patients ~~complete~~***are enrolled, then performed periodically at a frequency of approximately every 6 months. Additional interim analyses of efficacy and/or safety data may be performed during*** the study. ~~This analysis is planned~~ to support ~~the submission for accelerated approval.~~***regulatory and/or business objectives (such as informing future study designs).*** No adjustment to the type I error rate or CI coverage will be made to account for ***interim analyses. Details of*** the interim analysis~~.~~ ~~Following the formal interim analysis, interim~~	Revised language to clarify the role of planned interim analyses.	NS

		~~summaries of safety data will be performed periodically at a minimum frequency of every 6 months in order to report safety data from the ongoing study. The DSMB will meet regularly to~~ and its review ***process will be described in*** the ~~accumulating safety data~~***DSMB Charter.***		
11.9 Subgroup Analyses	Consistency of efficacy across important subgroups will be investigated within each cohort. At a minimum, primary efficacy will be summarized for subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, and baseline anti-fXa activity (above and below threshold cutoffs of 30 ng/mL, 50 ng/mL, and 75 ng/mL).	Consistency of efficacy across important subgroups will be investigated within each cohort. At a minimum, primary efficacy will be summarized for subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, ~~and~~ baseline anti-fXa activity ~~(~~***(categories (e.g.,*** above and below ~~threshold cutoffs~~thresholds of 30 ng/mL, 50 ng/mL, ~~and~~ 75 ng/mL~~).~~***), procedure type (e.g., orthopedic, abdominal, thoracic, neurosurgical), duration of surgery (≤ 2 hours, 2-4 hours, > 4 hours), and volume of blood loss (above and below the median). Other subgroup analysis may be considered based on the actual enrollment. Further detail of the subgroup analysis will be described in the Statistical Analysis Plan.***	Language added to describe additional subgroup analyses.	NS
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<table>
<tr><td></td><td></td><td><bi>10. van Diepen, S., et.al., Contemporary Management of Cardiogenic Shock: A Scientific Statement From the American Heart Association. Circulation, 2017. 136(16): p. e232-e268.</bi></td><td></td><td></td></tr>
<tr><td>Appendix F</td><td>N/A</td><td><bi>AMERICAN SOCIETY OF ANESTHESIOLOGISTS PHYSICAL STATUS CLASSIFICATION</bi>

<table><tr><td><bi>ASA PS 1</bi></td><td><bi>Normal healthy patient</bi></td></tr><tr><td><bi>ASA PS 2</bi></td><td><bi>Patients with mild systemic disease</bi></td></tr><tr><td><bi>ASA PS 3</bi></td><td><bi>Patients with severe systemic disease</bi></td></tr><tr><td><bi>ASA PS 4</bi></td><td><bi>Patients with severe systemic disease that is a constant threat to life</bi></td></tr><tr><td><bi>ASA PS 5</bi></td><td><bi>Moribund patients who are not expected to survive without the operation</bi></td></tr><tr><td><bi>ASA PS 6</bi></td><td><bi>A declared brain-dead patient whose organs are being removed for donor purposes</bi></td></tr></table><bi>ASA = American Society of Anesthesiology; PS = Physical Status</bi></td><td>Added to note ASA classifications.</td><td>NS</td></tr>
<tr><td>Appendix G</td><td>N/A</td><td>displayed</td><td>Added to summarize changes from the original protocol.</td><td>NS</td></tr>
</table>

Synopsis Dosing table (original):

Dose	Timing of Last Dose of FXa Inhibitor	Initial IV Bolus		Follow-on IV Infusion
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban ≤ 10 mg • Apixaban ≤ 5 mg • Enoxaparin ≤ 40 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery (extended infusion for longer surgeries)	Extended infusion (beyond 120 minutes) may be administered at **4 mg/min** (low-dose) for up to 4 additional hours*
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **Dose or Time Unknown**	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery (extended infusion for longer surgeries)	

Synopsis Dosing Table (revised):

***Andexanet* Dose**	**Timing of Last Dose of FXa Inhibitor**	**Initial ~~IV Bolus~~ *Dose***		**~~Follow-on IV~~ *Extended* Infusion**
		Initial IV Bolus	***Initial Follow-on IV Infusion***	
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban ≤10 mg • Apixaban ≤5 mg • Enoxaparin ≤40 mg • ***Edoxaban 30 mg***	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery ~~(extended infusion for longer surgeries)~~	Extended infusion (beyond 120 minutes) may be administered at **4 mg/min** (low-dose) for up to 4 additional hours*
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR ***> 15 hours or unknown time*** • ***Local anti-fXa > 100 ng/mL (0.5 IU/mL for enoxaparin)*** ~~**Dose or Time Unknown**~~	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery ~~(extended infusion for longer surgeries)~~	

SOA (original):

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	**1**								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Obtain Consent	X										
Determine Eligibility	X										
Obtain Medical History	X										
Obtain Prior Medications and Time of Last Anticoagulant Dose or Plasma Level	X										
Obtain ASA Class			X								
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X	X	X			
Weight (actual reported/recent)	X										
Physical Examination	X							X	X	X	X
Central Labs: Anti-fXa and anti-IIa Activity		X			X		X	X			
Central Labs: Thrombin Generation	X	X			X		X	X	X	X	

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	1								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Central Labs: Antibodies to andexanet, HCPs, and FX/FXa (modified Bethesda); and nAb (andexanet)	X										X
Central Labs: TFPI activity		X					X	X	X	X	X
Local Labs: PT-INR	X										
Local Labs: Chemistry and Pregnancy Test [3]	X										
Local Labs: CBC		X					X	X			X
Prepare andexanet (all patients)	X										
Administer andexanet Bolus, Immediately Followed by an Infusion			**Bolus + Infusion**								
Assess Need for Extended Andexanet Infusion.(if Surgery Ongoing)						X [4]					
Surgical Intervention				SURGERY							
Record Blood Loss Post Surgery							X				
Record Investigator Assessment of Intra-operative Hemostasis							X				

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	1								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Record Blood Products & Hemostatic Treatments [5]		X									
Record Bleeding-Related Diagnostic & Therapeutic Procedures [6]		X							X	X	
Record Volume of Colloid and Crystalloid [5]		X									
Record Hours in ED, ICU/Critical Care, General Hospital Floor, and Total as an Inpatient											X
Record AEs	X	X							X	X	X
Record Concomitant Medications	X	X							X	X	X
Ascertain Survival Status											X

AE = Adverse event; ASA = American Society of Anesthesiologists; BP = Blood pressure; CBC = Complete blood count; CRF = Case report form; CT = Computed tomography; d = Day(s); ED = Emergency department; EoS = End of Surgery; ET = Early Termination; FX = Factor X; FXa = Activated factor X; h = Hour(s); HCP = Host cell protein; HR = Heart rate; ICU = Intensive care unit; INR = International normalized ratio; IV = Intravenous; min = Minute(s); nAb = Neutralizing antibody (activity); PT = Prothrombin time; RR = Respiratory rate; SoS = Start of Surgery; Temp = Temperature; TFPI = Tissue factor pathway inhibitor

[1] Start of surgery is Time 0 and must be within 15 hours of the last FXa inhibitor dose.

[2] The EoS time point may occur before SoS + 1 hour or SoS + 2 hour; EoS procedures should be carried out when EoS occurs.

[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.

[4] Approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

[5] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.

[6] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.

SOA (revised):

	Screening & Baseline		**Treatment**					**Follow-Up**		
STUDY DAY:	**1**							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: ~~All time points relative to start of surgery~~	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	~~**SoS + 1 h**~~ ***End of Bolus*** ± 15 min	~~**SoS + 2 h ±**~~ ***EoII -15 min***	**EoS [~~2~~*1*] ~~±~~** +15 min ***[2]***	~~**SoS**~~ ***EoS*** **+ 12 h** ± 1 h	~~**SoS**~~ ***EoS*****+ 24 h** ± 1 h	~~**SoS**~~ ***EoS*** **+ 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Obtain Consent	X									
Determine Eligibility	X									
Obtain Medical History	X									
Demographics	***X***									
Obtain Prior Medications and Time of Last Anticoagulant Dose or Plasma Level	X									
Obtain ASA Class			X							
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X	X	X	***X***	***X***
Weight (actual reported/recent)	X									***X***
Physical Examination	X						X	X	X	X
Central Labs: Anti-fXa and anti-IIa Activity		X ***(pre-ADX)***		***X***	X	***X***	X	~~X~~		
Central Labs: Thrombin Generation	X	X ***(pre-ADX)***		***X***	X	***X***	X	X	X	~~X~~
Central Labs: Antibodies to andexanet, HCPs, and FX/FXa (modified Bethesda); and nAb (andexanet)	X ***(pre-ADX)***									***X***
Central Labs: TFPI activity		X ***(pre-ADX)***		***X***	***X***	***X***	X	X	X	X
Local Labs: PT-INR	X									
Local Labs: Chemistry and Pregnancy Test [3]	X									

	Screening & Baseline		**Treatment**					**Follow-Up**		
STUDY DAY:	**1**							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: ~~All time points relative to start of surgery~~	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	~~**SoS + 1 h**~~ ***End of Bolus*** ± 15 min	~~**SoS + 2 h ±**~~ ***EoII -15 min***	**EoS [~~21~~]** ~~±~~ +15 min ***[2]***	~~**SoS**~~ ***EoS*** **+ 12 h** ± 1 h	~~**SoS**~~ ***EoS*****+ 24 h** ± 1 h	~~**SoS**~~ ***EoS*** **+ 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Local Labs: CBC		X				***X***	X	~~X~~		***X***
Prepare ***A***ndexanet ~~(all patients)~~	X									
Administer ***A***ndexanet Bolus, Immediately Followed by an Infusion			~~**Bolus + Infusion**~~ ***X***							
Assess Need for Extended Andexanet Infusion.(if Surgery Ongoing)					X [4]					
Surgical Intervention				SURGERY						
Record Blood Loss Post Surgery						X				
Record Investigator Assessment of ~~Intra-operative~~ ***Intraoperative*** Hemostasis						X				
Record Blood Products & Hemostatic Treatments [5]		X								
Record Bleeding-Related Diagnostic & Therapeutic Procedures [6]		X						X	X	
Record Volume of Colloid and Crystalloid [5]		X								
Record Hours in ED, ***PACU,*** ICU/Critical Care, General Hospital Floor, and Total as an Inpatient										X
Record AEs	X	X						X	X	X
Record Concomitant Medications	X	X						X	X	X

	Screening & Baseline			**Treatment**				**Follow-Up**		
STUDY DAY:	**1**							**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: ~~All time points relative to start of surgery~~	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	~~**SoS + 1 h**~~ ***End of Bolus*** ± 15 min	~~**SoS + 2 h ±**~~ ***EoII -15 min***	**EoS [~~*21*~~]** ~~±~~ +15 min ***[2]***	~~**SoS**~~ ***EoS* + 12 h** ± 1 h	~~**SoS**~~ ***EoS*+ 24 h** ± 1 h	~~**SoS**~~ ***EoS* + 72 h** ± 1 h	+ 7 days
	These time points relative to start of surgery									
Ascertain Survival Status										X

AE = Adverse event; ASA = American Society of Anesthesiologists; BP = Blood pressure; CBC = Complete blood count; ~~CRF = Case report form; CT = Computed tomography; d = Day(s);~~ ED = Emergency department; ***EoII = End of Initial Infusion;*** EoS = End of Surgery; ET = Early Termination; FX = Factor X; FXa = Activated factor X; h = Hour(s); HCP = Host cell protein; HR = Heart rate; ICU = Intensive care unit; INR = International normalized ratio; ~~IV = Intravenous~~; min = Minute(s); nAb = Neutralizing antibody (activity); ***OR = operating room; PACU = Post-anesthesia care unit;*** PT = Prothrombin time; RR = Respiratory rate; SoS = Start of Surgery; Temp = Temperature; TFPI = Tissue factor pathway inhibitor

[1] ~~Start of surgery is Time 0 and must be within 15 hours of the last FXa inhibitor dose~~. ***The EoS time point before may occur SoS + 1 hour or SoS + 2 hour; EoS procedures should be carried out when EoS occurs.***

[2] ~~The EoS time point may occur before SoS + 1 hour or SoS + 2 hour; EoS procedures should be carried out when EoS occurs.~~ ***Collect EoS samples within 15 minutes from the end of surgery but before stopping infusion.***

[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.

[4] Approximately 30-45 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

[5] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.

[6] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.

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

PROSPECTIVE, OPEN-LABEL STUDY OF ANDEXANET ALFA IN PATIENTS RECEIVING A FACTOR XA INHIBITOR WHO REQUIRE URGENT SURGERY (ANNEXA-S)

DRUG NAME:	Andexanet alfa (PRT064445)
PROTOCOL NUMBER:	19-515
PHASE:	3b/4
TRIAL SPONSOR:	Portola Pharmaceuticals, Inc. PPD South San Francisco, CA 94080
MEDICAL MONITOR:	PPD, MD Medical Director Clinical Development Portola Pharmaceuticals, Inc. Phone: PPD Fax: PPD email: PPD
PROTOCOL DATE:	Original: 16 September 2019

Confidentiality Statement

This protocol is the property of Portola Pharmaceuticals, Inc. It is a confidential communication. Acceptance implies an agreement not to disclose information contained herein that is not otherwise publicly available, with the exception that it may be disclosed to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for the purpose of obtaining approval to conduct the study. The IRB/IEC is requested and expected to maintain confidentiality. This document may not be used or published without the consent of Portola Pharmaceuticals, Inc.

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulation (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Portola Pharmaceuticals, Inc.

Signature of Principal Investigator

Name of Principal Investigator (Print) Date (DD Month YYYY)

SPONSOR'S AGREEMENT

I have read the attached protocol entitled "Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 Code of Federal Regulations (CFR) Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

PPD

PPD , MD PPD

Med PPD irector
Clinical Development
Portola Pharmaceuticals, Inc.

17SEP2019
Date (DD Month YYYY)

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LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
andexanet alfa	Recombinant factor Xa inhibitor antidote, PRT064445
AUC	Area under the curve
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum observed concentration
CRF	Case report forms
CT	Computed tomography
D-dimer	Fibrin degradation product
DOAC	Direct Oral Anticoagulants
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EAC	Endpoint Adjudication Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Emergency department
EDC	Electronic data capture
ETP	Endogenous thrombin potential
F1+2	Prothrombin fragment 1+2
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FIO_2	Fraction of inspired oxygen
FX	Factor X
FXa	Factor Xa
GCP	Good Clinical Practice
HCP	Host-cell protein
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit

Term	Definition
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
min	Minute
MRI	Magnetic resonance imaging
nAb	Neutralizing antibody (activity)
PaO_2	Partial pressure oxygen-arterial
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic
PE	Pulmonary embolism
PK	Pharmacokinetic
PRBC	Packed red blood cell
PT	Prothrombin time
RBC	Red blood cell
rfVIIa	Recombinant factor VIIa
RR	Respiratory rate
SAE	Serious adverse event
SBP	Systolic blood pressure
t½	Half-life
TAT	Thrombin-antithrombin
TE	Thrombotic event
TEAE	Treatment-Emergent Adverse Event
Temp	Temperature
TF	Tissue factor
TFPI	Tissue factor pathway inhibitor
TG	Thrombin generation
TXA	Tranexamic acid
ULN	Upper limit of normal
VKA	Vitamin K antagonist
VTE	Venous thromboembolism
WBC	White blood cells

PROTOCOL SYNOPSIS

Study Title	Prospective, Open-label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who Require Urgent Surgery (ANNEXA-S)
Study Number	19-515
Study Phase	3b/4
Number of Sites	Approximately 120 sites in North America, Europe, and Rest of World
Objectives	In patients requiring urgent surgery who are being treated with a direct or indirect Factor Xa (FXa) inhibitor, the objectives of this study are as follows: **Primary Objective:** • To evaluate hemostatic efficacy following andexanet alfa (andexanet) treatment. **Secondary Efficacy Objective:** • To evaluate the effect of andexanet on anti-fXa activity. **Exploratory Efficacy Objectives:** • To evaluate the effect of andexanet on thrombin generation (TG). • To evaluate the use of red blood cell (RBC) transfusions. • To evaluate the use of non-RBC, non-platelet blood products and hemostatic agents. • To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir. • To evaluate the time from obtaining informed consent to the start of surgery. • To evaluate the length of index hospitalization, intensive care unit (ICU) stay, and length of surgery. • To evaluate the occurrence of re-hospitalization. • To evaluate the occurrence of post-surgical bleeding, including surgical wound hematomas. • To evaluate the occurrence of re-operations for bleeding. • To evaluate the effect of andexanet on tissue factor pathway inhibitor (TFPI). • In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity. **Safety Objective:** • To evaluate the overall safety of andexanet.
Efficacy Endpoints	**Primary Efficacy Endpoint:** • The achievement of hemostatic efficacy as determined by the surgeon's assessment of intra-operative hemostasis and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC). **Secondary Efficacy Endpoint:** • The percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion.

	Exploratory Endpoints: • Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, 12-hour nadir, number of patients with percent reduction from baseline > 80%. • Reversal of anticoagulant effect as measured by TG parameters (with endogenous thrombin potential as the primary measure). • Occurrence of receiving 1 or more RBC transfusions from the start of the andexanet bolus through 12 hours after the start of surgery. • The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the start of surgery. • The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the start of surgery. • Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the start of surgery. • Time from the signing of informed consent to the start of surgery. • Length of index hospitalization, assessed at the Day 30 visit. • Time hospitalized in an ICU, assessed at the Day 30 visit. • Length of surgery. • Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post enrollment). • Occurrence of post-surgical bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery. • Occurrence of re-operations for bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery. • Change from baseline in TFPI activity post-administration of andexanet. • Change from baseline in anti-IIa activity (only patients taking enoxaparin).
Safety Measurements	• Adverse events (AEs) (including serious AEs [SAEs]), vital signs, physical examinations, and clinical laboratory measurements. • Thrombotic events (TEs) within 30 days of enrollment, including suspected and confirmed by adjudication. • Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality. • Antibodies to FX, FXa, andexanet, and host-cell proteins (HCPs).
Study Design	This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery who have within 15 hours received their last dose of 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. If the time from last dose of FXa inhibitor is unknown, the patient is not eligible. Alternatively, if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin), the patient may be enrolled, irrespective of the time of the last dose (even if unknown). The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have sufficient anti-fXa activity levels. The start of the andexanet bolus must be within 15 hours following the last dose of FXa inhibitor. Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an intravenous (IV) bolus administered over 15 to 30 minutes (depending on

Study Design (cont'd)	dose); the bolus will be followed by an IV infusion that will continue for 2 hours, irrespective of the duration of the surgery. The bolus will begin prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision; designated Time 0). Additional andexanet, be it for re-dosing or extended infusion, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-operative complications are met (see "Test Product, Dose, and Mode of Administration" below). The independent EAC will adjudicate all deaths, TEs, post-surgical bleeding events (e.g., surgical hematomas), and hemostatic efficacy. The independent EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter. All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit.

Study Periods	The study duration for any individual patient will be up to 37 days. There are 4 study periods. Study periods are defined as follows:
	• Screening Period: < 1 day (Day 1).
	• Pre-surgical Assessment Period: < 1 day (Day 1).
	• Treatment Period: < 1 day (Day 1).
	  o Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~2.5 hours) but no greater than a total 6 hours (including both the initial regimen and the extended infusion).
	  o Re-Dosing < 1 day, Day 1 or 2 (initiation occurs within 24 hours after the completion of the first course of andexanet treatment if applicable.)
	• Safety Follow-up Period: 30 + 7 days (Days 1–30 + 7).

Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or their medical proxy (or legal designee) has given written informed consent. 2. Age ≥ 18 and < 85. 3. Requires urgent surgical intervention that must occur within 12 hours of clinical presentation, for which reversal of anti-fXa activity is judged necessary. 4. Received 1 of the following FXa inhibitors within 15 hours prior to start of surgery: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d), OR if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin), the patient may be enrolled, irrespective of the time of the last dose. 5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential). 6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).
Exclusion Criteria	If a patient meets any of the following criteria, he or she is not eligible: 1. Surgery predicted to last > 4 hours or for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low. 2. Acute life-threatening bleeding at the time of screening. 3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the intra-operative use of systemic, intravascular, unfractionated heparin. 4. Expected survival of < 1 month due to comorbidity. 5. Existing "Do Not Resuscitate" order or similar advanced directive.

Exclusion Criteria (cont'd)	6. The patient has a recent history (within 30 days prior to screening) of a diagnosed TE as follows: venous thromboembolism (including deep vein thrombosis, pulmonary embolism, intracardiac thrombus), myocardial infarction (including asymptomatic troponin elevations), disseminated intravascular coagulation, acute traumatic coagulopathy, cerebrovascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease. 7. Acute decompensated heart failure or cardiogenic shock at the time of screening. 8. The patient has severe sepsis or septic or severe hemorrhagic shock at the time of Screening. 9. The patient is pregnant or a lactating female. 10. The patient has received any of the following drugs or blood products within 7 days of enrollment: o Vitamin K antagonist (e.g., warfarin). o Dabigatran. o Prothrombin complex concentrate products (e.g., Kcentra®) or recombinant factor VIIa (e.g., NovoSeven®). o Whole blood, plasma fractions. Note: Administration of tranexamic acid, platelets or packed red blood cells is not an exclusion criterion. 11. The patient was treated with an investigational drug < 30 days prior to Screening. 12. Prior treatment with andexanet.

Test Product, Dose, and Mode of Administration

The andexanet IV bolus will be initiated within 30 minutes prior to the start of surgery (i.e., the first incision). The bolus will be followed by a continuous infusion lasting 120 minutes, irrespective of the length of the surgery. It is possible that the bolus or continuous infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens as described below:

Dose	Timing of Last Dose of FXa Inhibitor	Initial IV Bolus	Follow-on IV Infusion
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban ≤ 10 mg • Apixaban ≤ 5 mg • Enoxaparin ≤ 40 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery (extended infusion for longer surgeries)
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR **Dose or Time Unknown**	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery (extended infusion for longer surgeries)

Extended Infusion

Following the primary andexanet bolus and infusion (~2.5 hours), the andexanet infusion will be continued at the low dose of andexanet (4 mg/min) if the surgery and immediate post-operative period extend longer than the primary bolus and infusion. The extended infusion will continue through the end of the surgery and the immediate post-operative period, not to exceed 6 hours total.

Criteria for Re-Dosing with Andexanet

Consider re-dosing with andexanet (low-dose bolus + infusion) only if:

a) New, clinically significant, surgery-related post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND

b) The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND

c) Re-dosing initiation occurs within 12 hours after the start of the first course of andexanet treatment.

Reference Therapy, Dose, and Mode of Administration

Not applicable.

Sample Size	**Total Enrollment Approximately 200 Patients** It is estimated that a sample size of 180 patients will provide approximately 89% power to reject the null hypothesis that 67% of the patients will achieve effective hemostasis. This power calculation assumes the true rate of achieving effective hemostasis is 77%. An approximate 10% attrition rate is expected (e.g., canceled surgeries, discontinued and/or non-evaluable patients). Therefore, 200 patients will be enrolled.
Statistical Analysis Methods for Efficacy	All efficacy analyses will be performed in the Efficacy Analysis Population. All hypothesis tests and confidence intervals (CI) will be 2-sided with α=0.05. The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI. The null and alternative hypotheses tested to support this analysis are: H_0: $\pi = 0.67$ H_1: $\pi \neq 0.67$ The study will be considered to have met its primary efficacy objective if the proportion of patients with effective hemostasis is statistically significantly higher than 67% ($p < 0.05$) using a 2-sided Chi-Square test with $\alpha = 0.05$, or the lower bound of the 2-sided 95% CI is greater than 0.67. The secondary endpoint, percent change in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. If the lower limit of the nonparametric CI for the median exceeds 0, the corresponding objective will be considered to have been met. For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.
Statistical Analysis Methods for Safety	Safety will be assessed by examination of 30-day survival status, AEs (including SAEs and TEs), vital signs, clinical laboratory measurements, and antibodies to andexanet, FX, FXa, and HCPs. These data will be descriptively summarized. All potential post-surgical bleeding events and TEs will be confirmed by adjudication.

1.0 INTRODUCTION

1.1. Background

The class of oral anticoagulants known as direct Factor Xa (FXa) inhibitors (Direct Oral Anticoagulants [DOACs]) has consistently demonstrated comparable or superior efficacy and/or safety relative to its predecessors, Vitamin K Antagonists (VKAs) and Low Molecular Weight Heparins. These agents (apixaban [Eliquis®], betrixaban [BevyxXa®], edoxaban [Savaysa®], rivaroxaban [Xarelto®]) are approved for the prevention of serious thromboembolic outcomes (e.g., stroke, deep vein thrombosis [DVT], pulmonary embolism [PE], venous thromboembolism [VTE] in hip or knee replacement surgery) and have become widely used in the United States (US) and globally. One limitation to the use of FXa inhibitors has been the lack of an antidote to be used in cases of severe and/or life-threatening bleeding events or urgent or emergency surgery. In the case of the latter, it has been estimated, based on analyses from pivotal studies of oral anticoagulants, that approximately 1% of anticoagulated patients may require urgent surgery within 2 years of initiation [1, 2]. As the use of DOAC agents increase, the need to reverse anticoagulation related to this class of drugs is expected to increase.

Andexanet, a rationally designed, recombinant analog of endogenous human FXa, has been developed to rapidly and potently reverse FXa inhibition and restore physiologic coagulation. Data from Phase 2, Phase 3, and ongoing Phase 3b/4 studies have shown that andexanet rapidly reverses FXa inhibition in healthy volunteers and in bleeding patients [16]. Andexanet is also associated with a high rate of clinical hemostasis in patients with acute major bleeding [4]. Importantly, however, andexanet has not been evaluated in patients requiring urgent surgery. The present trial will be performed to demonstrate improved hemostatic efficacy with andexanet in patients requiring urgent surgery receiving an oral FXa inhibitor.

Andexanet was granted accelerated approval by the US Food and Drug Administration (FDA) on 03 May 2018 and was granted conditional marketing authorization by the European Commission on 26 April 2019, for the treatment of patients with life-threatening bleeding while taking apixaban and rivaroxaban. The confirmatory randomized controlled trial in patients with intracranial hemorrhage, ANNEXA-I, is currently ongoing. Andexanet is not currently indicated for FXa reversal in patients requiring urgent surgery.

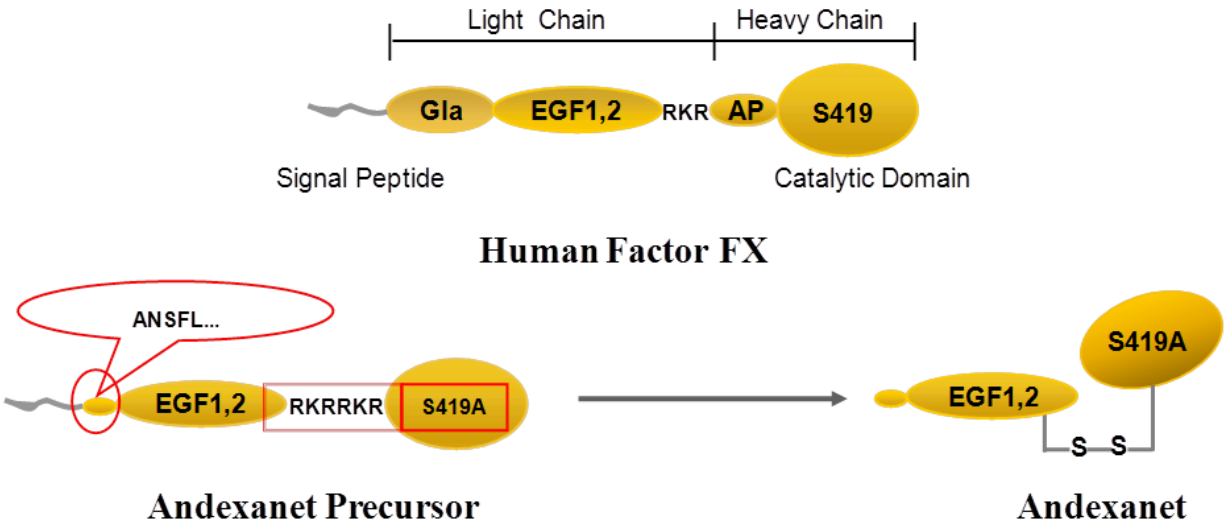
1.2. Description of Andexanet

Andexanet is a recombinant version of human FXa that has been modified to render it functionally inactive (Figure 1). To achieve this aim, 2 key structural modifications were made to native human FXa. First, the substitution of a serine residue with an alanine at the active site eliminated the protein's catalytic activity. Second, the removal of the Gla domain eliminated the ability to assemble into a prothrombinase complex, thereby removing potential intrinsic anticoagulant effects. Reversal of anticoagulation is achieved because andexanet retains the

ability to bind FXa inhibitors with high affinity, thereby sequestering them and preventing them from binding to and inhibiting native FXa.

Additional information about the mechanism and structure of andexanet can be found in the Investigator's Brochure.

Figure 1: Structures of Human Factor X and Andexanet



1.3. Summary of Relevant Nonclinical Experience with Andexanet

Nonclinical studies in several species (mice, rats, rabbits, pigs, and cynomolgus monkeys) have demonstrated that the anticoagulant effects of direct and indirect FXa inhibitors were reversed by andexanet, resulting in a return to normal hemostasis.

Functional studies with the direct FXa inhibitors have been undertaken to explore the effectiveness of andexanet to reverse injury-induced bleeding in anticoagulated animals using the well-characterized rodent tail transection models and a modified rabbit liver laceration model. In these studies, andexanet was administered either prior to (prophylactic model) or following (treatment model) organ injury to mimic the clinical settings of urgent (emergent) surgery or massive bleeding as a result of trauma. In both the prophylactic and treatment models, significant reductions in blood loss were observed in andexanet-treated animals vs vehicle controls. The decrease in blood loss following andexanet administration correlated with a decrease in pharmacodynamics (PD) markers of anticoagulation, including anti-fXa activity, international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time, depending on the inhibitor and species. Collectively, in these models, andexanet dose-dependently reduced the anticoagulant effects of the direct FXa inhibitors, requiring a minimum molar ratio of ~1:1, andexanet:direct FXa inhibitor for maximal inhibition of anti-fXa activity.

Andexanet has also been tested in a pig polytrauma model designed to evaluate its efficacy in a setting with a greater severity of bleeding. Using German landrace pigs anticoagulated with apixaban (20 mg/day for 4 days), the effect of an intravenous (IV) bolus (1,000 mg) of andexanet versus a bolus (1,000 mg) plus a 2-hour infusion (10 mg/min) was studied when andexanet was administered after crush injury to a single lobe of the liver, followed by bilateral femur fracture. Following andexanet treatment (12 minutes after injury) with a bolus alone, there was a rapid drop in anti-fXa levels to near zero, which returned to placebo levels ~2 hours later. With bolus plus infusion, the anti-fXa levels remained low throughout the duration of the infusion and then gradually returned to placebo levels approximately 2 hours after the end of infusion. With regard to bleeding, anticoagulation with apixaban resulted in an approximately 2-fold increase in blood loss 12 minutes after injury. In the control group (administered placebo), there was a subsequent increase in blood loss over time to 3,403 ± 766 mL, and 100% of the animals exsanguinated with a mean survival time of 135 minutes (range 92–193 minutes). Treatment with andexanet resulted in a significant reduction in total blood loss post-injury: 57% (1,264 ± 205 mL) and 59% (1,202 ± 94 mL) for bolus alone and bolus plus infusion of andexanet, respectively. All andexanet-treated animals survived for the duration of the observation period (5 hours).

The toxicology of andexanet was evaluated in both rats and monkeys. Because the intent was to administer andexanet to reverse the anticoagulant effect of FXa inhibitors and thereby restore baseline hemostasis, studies in monkeys were conducted with andexanet administered alone as well as co-administered with FXa inhibitors. Andexanet was well-tolerated in both species at all dose levels. The highest dose administered in both species was 60 mg/kg/day (single day [only in monkeys] and 2-week repeat dose studies) and was the No Observed Adverse Effect Level. In monkeys the 60 mg/kg/day dose resulted in exposure levels 2-3-fold above those observed in clinical studies at the high therapeutic dose.

1.4. Summary of Relevant Clinical Experience with Andexanet

Andexanet has been studied in approximately 545 healthy subjects thus far in Phase 1 to 3 studies, as well as in 352 patients presenting with an acute major bleeding event while receiving an FXa inhibitor in the ongoing Phase 3b/4 (ANNEXA-4) study. In addition, andexanet was administered to a single preoperative patient taking apixaban who required emergency surgery to treat necrotizing fasciitis. Finally, there are 5 other ongoing studies; 4 in healthy volunteers: a Phase 2 study to investigate the reversal of the pharmacologic effects of the oral FXa inhibitor, betrixaban; a Phase 2 study to evaluate the pharmacokinetics (PK), PD, safety, and tolerability of andexanet in individuals of Japanese descent; and 2 Phase 1 studies to compare the PK of andexanet produced by 2 manufacturing processes; and 1 study in patients: a randomized controlled clinical trial to evaluate the clinical efficacy and safety of andexanet in patients with intracranial hemorrhage while taking direct FXa inhibitors.

Completed trials include a single ascending dose Phase 1 study (Study 11-501) in 32 healthy subjects; a Phase 1 study (Study 14-506) examining the PK and PD of andexanet in 10 young vs. 10 older subjects receiving apixaban; a Phase 1 PK/PD study (Study 16-512) to evaluate the PK, PD, safety, and tolerability of andexanet produced by an updated manufacturing process (Generation 2); a Phase 2 dose-ranging study (Study 12-502) in 152 healthy subjects to determine the appropriate doses to reverse the anticoagulant effects of apixaban, rivaroxaban, enoxaparin and edoxaban; and 2 Phase 3 studies in 148 healthy older subjects (50-75 years) to confirm that the doses defined in the Phase 2 study reverse apixaban (Study 14-503) and rivaroxaban (Study 14-504). Details of the completed studies may be found in the Investigator's Brochure.

1.4.1. Phase 1 Study of Andexanet Alone in Healthy Subjects (11-501)

Study 11-501 was a Phase 1 randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in 32 healthy subjects, each of whom received 1 of 4 doses of andexanet (30 mg, 90 mg, 300 mg, or 600 mg) (n=24) or placebo (n=8). The safety data from this study are summarized in Section 1.4.6.

1.4.2. Phase 1 Study of Andexanet in Healthy Younger Versus Older Subjects (14-506)

Study 14-506 was a Phase 1 non-randomized, open-label study of andexanet in healthy younger (18-45 years of age) subjects and healthy older (≥ 65 years of age) subjects. Ten younger and 10 older subjects were enrolled, with all subjects dosed to steady-state with apixaban then receiving a 400 mg bolus of andexanet. In this study, the PK of andexanet and the PD effects on anti-fXa activity and thrombin generation (TG) in older and younger subjects were similar. The safety data from this study are summarized in Section 1.4.6.

1.4.3. Phase 1 PK/PD Study to Evaluate the PK, PD, Safety, and Tolerability of Andexanet Produced by an Updated Manufacturing Process (Generation 2) (16-512-Direct Inhibitors)

Study 16-512-Direct Inhibitors was a randomized, double-blind, study in healthy volunteers dosed to steady state with FXa inhibitors, designed to: 1) demonstrate PK and PD comparability between andexanet manufactured by the Generation 1 and Generation 2 processes; 2) evaluate the degree to which Generation 2 andexanet reverses FXa-inhibitor-induced anticoagulation in comparison to placebo; and 3) evaluate the safety and tolerability of Generation 2 andexanet. A total of 122 subjects were enrolled in the study. Generation 1 and Generation 2 andexanet were found to have PK comparability when administered at low doses, though strict bioequivalence criteria were not met with high dose andexanet. That said, Generation 1 and Generation 2 andexanet were observed to be comparable for the primary PD parameter of anti-fXa activity at both low and high doses of andexanet. The safety data from this study are summarized in Section 1.4.6.

1.4.4. Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects (12-502)

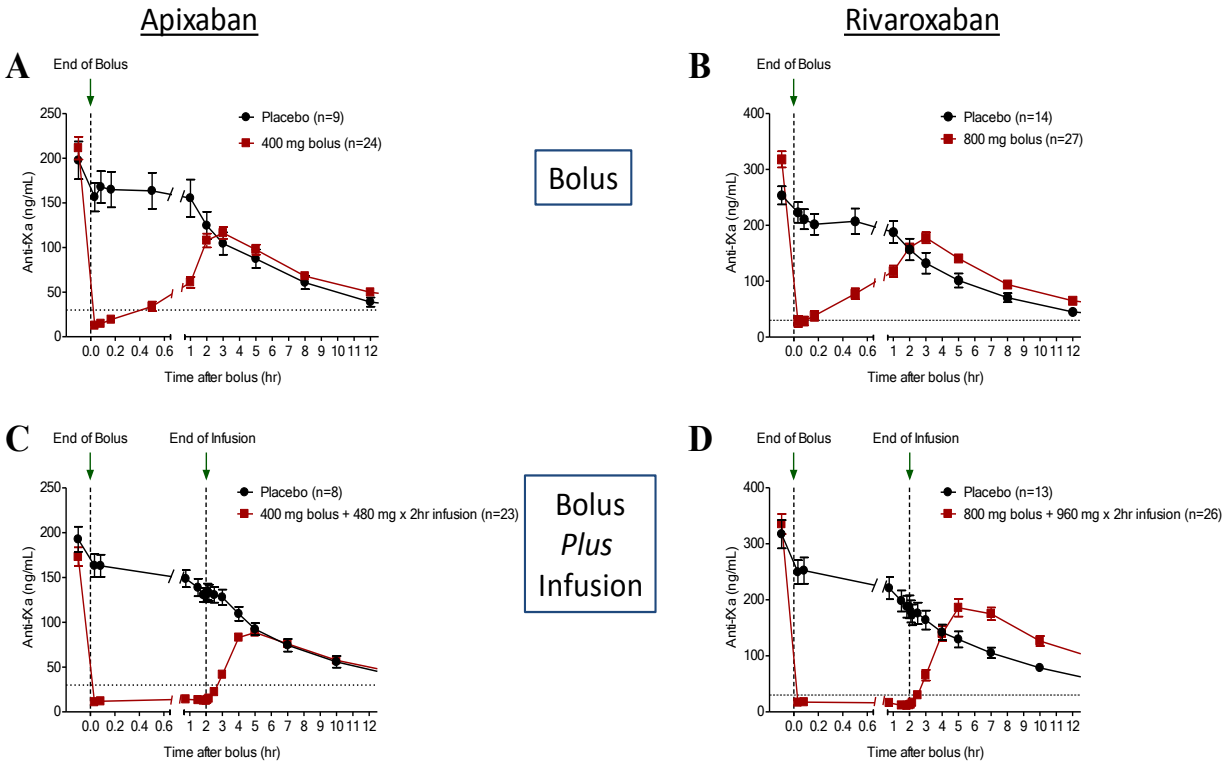
The dose-finding Study 12-502 was a Phase 2, randomized, double-blind, placebo-controlled study of the safety, PK, and PD of andexanet in healthy subjects receiving 1 of 4 direct or indirect FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Each FXa inhibitor was examined in a separate study module, within which multiple dosing regimens of andexanet were given in cohorts of 9 healthy subjects (6 active, 3 placebo). The anticoagulant was dosed to steady state over 5 to 6 days, before administration of andexanet or placebo on Study Day 6. Depending on the anticoagulant dose, the total dose of andexanet across dosing cohorts ranged from 90 to 1,760 mg. Healthy subjects were then followed through Study Day 13 in a domiciled Phase 1 study unit and, subsequently, through Day 48 as outpatients.

Andexanet exhibited dose-proportional PK for both C_{max} (maximum observed concentration) and AUC (area under the curve) with a mean terminal half-life ($t_{½}$) of approximately 8 hours. Administration of andexanet also resulted in a dose-dependent reduction in anti-fXa activity for each of the FXa inhibitors. Additionally, the downstream anticoagulant effects of apixaban, rivaroxaban, and edoxaban were reversed in a dose-dependent fashion by administration of andexanet, as evaluated by the measurement of TG. These effects were consistent with restoration of hemostatic mechanisms after andexanet administration. The safety data from this study are summarized in Section 1.4.6.

1.4.5. Phase 3 Studies in Healthy Older Volunteers (14-503 and 14-504)

Two randomized, double-blind, placebo-controlled studies were designed to evaluate reversal of anticoagulation in older subjects (ages 50-75 years) anticoagulated with apixaban (Study 14-503) or rivaroxaban (Study 14-504). In these studies, the anticoagulant was dosed to steady state over 4 days (rivaroxaban) or 3.5 days (apixaban) before administration of andexanet or placebo on Study Day 4. The subjects were then followed through Study Day 8 in a domiciled Phase 1 study unit and, subsequently, through Day 43 as outpatients. Andexanet was administered either as an IV bolus (Part 1) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). Reversal of anticoagulation was measured using anti-fXa activity, anticoagulant free fraction, TG, and other coagulation markers. A single IV bolus of andexanet significantly reversed the anti-fXa activity of apixaban and rivaroxaban, reduced unbound apixaban and rivaroxaban concentrations, and restored normal TG (Figure 2), with the maximal effect observed within 2 minutes of the end of the bolus administration. The safety data from this study are summarized in Section 1.4.6.

Figure 2: Rapid Onset and Significant Reduction of Apixaban and Rivaroxaban Anti-fXa Activity in Older Healthy Subjects by Andexanet (Study 14-503 and Study 14-504)



Legend: Anti-fXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion.

A. Apixaban – with andexanet 400 mg IV bolus
B. Rivaroxaban – with andexanet 800 mg IV bolus
C. Apixaban – with andexanet 400 mg IV bolus plus 4 mg/minute infusion for 120 minutes
D. Rivaroxaban – with andexanet 800 mg IV bolus plus 8 mg/minute infusion for 120 minutes

Note: A break in the X axis was added to better visualize the immediate, short-term dynamics of anti-fXa activity following andexanet treatment. The points on the graph represent the mean anti-fXa activity level and error bars illustrate standard error. There was a statistically significant difference ($P < 0.05$) in the percent change of anti-fXa activity normalized to pre-bolus between andexanet and placebo until 2 hours after administration of bolus (Part 1) or infusion (Part 2). The horizontal dashed-line represents the anti-fXa activity at 30 ng/mL, the estimated non-effective level for FXa inhibition [5].

1.4.6. Summary of Safety from Clinical Studies of Healthy Subjects

Andexanet has been generally well tolerated in healthy volunteers in the Phase 1, 2, and 3 studies at single doses up to 1,760 mg, with no apparent pattern of safety signals with the exception of mild-moderate infusion reactions. A single adverse event (AE) (bilateral pneumonia) met serious adverse event (SAE) criteria in the Phase 1 study 11-501. This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred 18 days after dosing.

No severe or life-threatening AEs have been reported. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent, and have rarely required treatment (2 subjects received 1 dose each of diphenhydramine). With the exception of 2 subjects in the Phase 1 study who received a 90 mg dose of andexanet, infusion reactions have not led to premature discontinuation of andexanet at doses of up to 1,760 mg total dose. Therefore, to date, infusion reactions have not been dose-limiting.

Andexanet was associated with dose-dependent increases in prothrombin fragment 1 and 2 (F1+2), thrombin-antithrombin (TAT), and fibrin degradation product (D-dimer), and with a concomitant decrease in tissue factor pathway inhibitor (TFPI) activity, all of which reversed quickly after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with clinical evidence of thrombosis. Compared with administration of andexanet alone (Study 11-501), the effects on F1+2, TAT, D-dimer, and TFPI were attenuated (all to a similar extent) in the presence of an anticoagulant.

In all completed studies to date, among healthy subjects treated with andexanet, 10-12% developed low-titer non-neutralizing antibody (nAb) to andexanet. There have been a small number of very low-titer non-nAbs to FX and FXa, with the titer value for all positive samples occurring at the minimum required dilution. However, there have been no nAbs to FX or FXa.

1.4.7. Phase 3b/4 Study in Patients with Acute Major Bleeding (14-505)

Study 14-505 (ANNEXA-4) is an ongoing, multi-national, prospective, open-label, single-arm clinical study of andexanet in patients with acute major bleeding while taking an FXa inhibitor (specifically apixaban, edoxaban, enoxaparin, or rivaroxaban). As of 01 June 2018, 352 patients had been enrolled in the study. Baseline characteristics included a mean age of 77 years, 47% female, 87% Caucasian, and median body mass index 27 kg/m^2. A total of 90 patients (26%) had gastrointestinal or urinary bleeding, 227 patients (64%) had an intracranial hemorrhage, and 35 patients (10%) had other types of bleeding.

Of the 352 enrolled patients, 254 were considered efficacy evaluable, defined as having a major bleed confirmed by adjudication, and a baseline anti-fXa activity of 75 ng/mL or greater ($\geq$ 0.25 IU/mL for enoxaparin patients). In efficacy-evaluable patients taking apixaban and rivaroxaban, the median reduction from baseline in anti-fXa activity was > 90%. Overall, of 249 patients with evaluable hemostatic efficacy, 204 (81.9%) had excellent or good hemostatic efficacy. Of these, 171 (68.7%) were adjudicated as having excellent hemostatic efficacy and 33 (13.3%) as having good hemostatic efficacy. Of the efficacy evaluable patients presenting with intracranial hemorrhage, the rate of excellent or good hemostatic efficacy was 80.4%.

Of the 352 patients in the Safety Population, 250 patients (71.0%) experienced at least 1 treatment-emergent AE (TEAE). The most frequently reported TEAEs (occurring in ≥ 5% of patients) by preferred term were urinary tract infection in 31 patients (8.8%) and pneumonia in 21 patients (6.0%). A total of 32 patients (9.1%) experienced AEs that were considered by the Investigator to be possibly or probably related to andexanet. The most frequent treatment-related events were pyrexia (4 patients; 1.1%), ischemic stroke (4 patients; 1.1%), and headache and nausea (3 patients each; 0.9%).

Serious adverse events were experienced by 144 patients (40.9%). The most common SAEs (occurring in ≥ 2% of patients) were pneumonia in 11 patients (3.1%) and respiratory failure in 9 patients (2.6%). Seventeen (4.8%) patients experienced at least 1 treatment-related SAE. The most frequently reported SAEs that were considered by the Investigator to be possibly or probably related to andexanet were ischemic stroke (3 patients; 0.9%), and DVT, myocardial infarction, cerebral infarction, cerebrovascular accident, and PE (2 patients each; 0.6%).

There have been 54 deaths (15.3%) prior to the Day 30 visit; of these, 37 were adjudicated as cardiovascular deaths and 12 as non-cardiovascular deaths. Overall, the mortality rate was consistent with the expected burden of AEs in this patient population given the vascular risk factors, overall high morbidity, and poor prognosis of patients with acute major bleeding.

A total of 34 patients (9.7%) with any bleeding type experienced an adjudicated clinical thrombotic event (TE). While re-anticoagulation rates were similar between patients with and without TEs, the time to resumption of anticoagulation was markedly greater in patients with TEs.

No clinically meaningful changes in laboratory values related to andexanet (including hematocrit and hemoglobin) were detected in the study. Similarly, no clinically significant changes in vital signs and/or physical examination findings have been observed. Finally, no nAbs to FX, FXa, or andexanet have been detected in the study.

A randomized clinical trial (Study 18-513, ANNEXA-I) is currently underway to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracranial hemorrhage.

2.0 STUDY OBJECTIVES

In patients requiring urgent surgery who are being treated with a direct or indirect FXa inhibitor, the objectives of this study are described in the subsections that follow.

2.1. Primary Objectives

- To evaluate the hemostatic efficacy following andexanet treatment.

2.2. Secondary Efficacy Objectives

- To evaluate the effect of andexanet on anti-fXa activity.

2.3. Exploratory Efficacy Objectives

- To evaluate the effect of andexanet on TG.
- To evaluate the use of red blood cell (RBC) transfusions.
- To evaluate the use of non-RBC, non-platelet blood products, and hemostatic agents.
- To evaluate the transfusion-corrected change in hemoglobin from baseline to the nadir.
- To evaluate the time from obtaining informed consent to the start of surgery.
- To evaluate the length of index hospitalization, intensive care unit (ICU) stay, and length of surgery.
- To evaluate the occurrence of re-hospitalization.
- To evaluate the occurrence post-surgical bleeding, including surgical wound hematomas.
- To evaluate the occurrence of re-operations for bleeding.
- To evaluate the effect of andexanet on TFPI.
- In patients receiving enoxaparin, to evaluate the effect of andexanet on anti-IIa activity.

2.4. Safety Objectives

- To evaluate the overall safety of andexanet.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a multicenter, prospective, open-label study of andexanet alfa (referred to subsequently as "andexanet") to determine the efficacy and safety of andexanet in patients who require urgent surgery (must occur within 12 hours of clinical presentation) who have, within 15 hours, received 1 of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin.

The start of the andexanet bolus must be within 15 hours following the last dose of FXa inhibitor. If the time from last dose of FXa inhibitor is unknown, the patient is not eligible, unless a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for patients taking enoxaparin), in which case the patient may be enrolled, irrespective of the time of the last dose (even if unknown). The prespecified time periods and/or anti-fXa activity levels are designed to ensure patients have therapeutic anti-fXa activity levels.

Patients will receive 1 of 2 dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose of FXa inhibitor. Patients will receive an IV bolus of andexanet administered over 15 to 30 minutes (depending on dose), followed immediately by an IV continuous infusion of andexanet for 2 hours, irrespective of the duration of surgery. The bolus will begin prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision; designated as Time 0). It is possible that the bolus or continuous infusion may be ongoing at the start of surgery. Additional andexanet, be it for extended treatment or re-dosing, may be given at the discretion of the Investigator when specific criteria regarding duration of surgery and/or intra-operative complications are met (see Section 6.2).

Prior to surgery, the American Society of Anesthesiologists classification for each patient will be recorded.

The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the surgeon's assessment of intra-operative hemostasis using a pre-specified 4-point scale (Section 11.5.1) and confirmed by adjudication by an independent Endpoint Adjudication Committee (EAC).

In addition to hemostatic efficacy, the EAC will adjudicate all deaths, TEs, and post-surgical bleeding events (e.g., surgical hematomas). The EAC will be blinded to all anti-fXa levels. An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB charter.

All AEs, including SAEs, and survival will be followed through the Day 30 post-treatment visit. The study schedule of activities can be found in Appendix A.

3.2. Blinding and Randomization

3.2.1. Randomization

There is no randomization in this study. All eligible patients will be enrolled and receive open-label andexanet treatment.

3.2.2. Blinding

This study will be open-label. However, the EAC will be blinded to all anti-fXa levels.

3.3. Duration of Study

The duration of the study for any individual patient will be up to 37 days.

There are 4 study periods. Study periods in the study for the respective cohorts are defined as follows:

- Screening Period: < 1 day (Day 1).
- Pre-surgical Assessment Period: < 1 day (Day 1).
- Treatment Period: < 1 day (Day 1).
    - Additional dosing during extended surgeries beyond initial andexanet dosing regimen (~ 2.5 hours) but no greater than a total of 6 hours (including both the initial regimen and the extended infusion).
    - Re-dosing < 1 day, Day 1 or 2 (initiation occurs within 24 hours after the completion of the first course of andexanet treatment if applicable [refer to Section 6.2]).
- Safety Follow-up Period: 30 + 7 days (Days 1–30 + 7).

3.4. Discussion of Study Design, Including Choice of Control

3.4.1. Study Population

The study will enroll patients between the ages of 18 and 85 who have recently taken an FXa inhibitor (i.e., within 15 hours prior to surgery or if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL [> 0.5 IU/mL for enoxaparin]) and who require urgent surgery for which reversal of anti-fXa activity is judged necessary.

Only patients who are in need of surgery that, in the opinion of the Investigator, cannot be delayed by 12 hours are to be enrolled. Procedures that are associated with a low bleeding risk are not eligible.

3.4.2. Rationale for the Dose Regimen

All patients will receive 1 of 2 doses of andexanet based on the specific anticoagulant taken and timing of the last dose.

The andexanet dosing regimens to be examined in this study are as follows:

- Low dose: 400 mg IV bolus at a rate of 30 mg/min (duration of approximately 15 minutes) followed by a continuous infusion at a target rate of 4 mg/min for 120 minutes irrespective of the duration of surgery (extended infusion at the discretion of the Investigator).
- High dose: 800 mg IV bolus at a rate of 30 mg/min (up to 30 minutes) followed by a continuous infusion at a target rate of 8 mg/min for 120 minutes irrespective of the duration of surgery (extended infusion at the discretion of the Investigator).

Data from the Phase 3 studies with apixaban and rivaroxaban, as well as a recently completed Phase 1 study of Generation 2 andexanet in healthy volunteers (Study 16-512-Direct Inhibitors; Section 1.4.3), confirm the levels of FXa inhibition and recovery of TG observed in the Phase 2 study. These doses of andexanet correspond to decreases in anti-fXa activity that correlate with normalization of hemostasis as measured by a TG assay. The change to the lower dose (400 mg) at 8 hours after the last administered FXa inhibitor dose was based on the PK-PD model that predicted the time at which equivalent anti-fXa activity reversal and TG normalization would be achieved.

In addition to the above, the doses for this study (19-515) were shown to substantially reduce anti-fXa activity and increase TG in a Phase 3b/4 study in which andexanet was given to patients receiving an FXa inhibitor who had acute major bleeding (ANNEXA-4).

3.4.3. Rationale for Extended Infusion or Re-Dosing of Andexanet

In this study, there is potential for patients to require additional andexanet treatment beyond what is initially stipulated for patients. For example, unpredictable events during surgery may prolong the procedure longer than the 4-hour estimated limit. In addition, a surgical patient may bleed after completion of surgery. Therefore, extended andexanet infusions (to address longer surgeries) and re-dosing of andexanet (for post-surgical bleeding events) will be implemented in the protocol.

A low-dose continuous infusion (4 mg/min) was selected as the regimen to use for extended infusions, whereas a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes) will be used for re-dosing. The rationale for these dosing levels is based on the premise that the amount of reversal agent required to neutralize an FXa inhibitor diminishes as the inhibitor is eliminated over time.

Investigators will be required to document in the case report form (CRF) the clinical justification for why subjects require extended infusion of andexanet or additional dosing of andexanet during surgery. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for extended duration of dosing or re-dosing during surgery are outlined in Section 6.2.

3.5. Safety Plan and Monitoring

The study will be conducted in patients who, by virtue of their condition, will typically be hospitalized or will be seen initially in the emergency department. As such, treatment with andexanet and subsequent monitoring will be done in a medical setting. It is expected that patients requiring urgent surgery will remain hospitalized for at least 12 hours, the timeframe for the primary efficacy evaluations. During the first 12-hour period (Study Day 1), AEs, vital signs, physical examinations, and laboratory testing will be performed as indicated in Appendix A to monitor safety. Survival status will be ascertained on Study Day 30, and cause of death will be recorded. Antibody samples will be taken at baseline and Day 30 to assess immunogenicity against andexanet, FX, FXa, and host-cell proteins (HCPs).

Of the 352 patients, 9.7% of patients with acute major bleeding in ANNEXA-4 experienced protocol-defined, adjudicated TEs that occurred within 30 days of andexanet treatment. While the attributability of these events to andexanet is uncertain, it is significantly possible that they will occur in the current study, given the anticipated enrolled population, for which reversal of anticoagulation may expose the underlying risk of TEs, and andexanet's known effects on coagulation biomarkers such as D-dimer, F1+2, and TFPI. In this study, patients with TEs within 30 days of Screening, those with a history of hypercoagulable states, and those who received procoagulant products within 7 days of Screening will not be eligible for the study due to their much greater risk for TEs in general and following anticoagulation reversal. In this study, TEs will be considered AEs of special interest (AESIs) and will be reported within 24 hours to the Sponsor. Thrombotic events, both suspected and confirmed by adjudication, will be tracked as safety endpoints for the study. To mitigate the risk of TEs, Investigators are encouraged to consider resumption of an anti-thrombotic agent as soon as it is clinically appropriate.

Prior and ongoing clinical studies have identified infusion reactions of mild or moderate intensity as an AE related to administration of andexanet (described in Section 1.4.5). Patients in this study will receive andexanet in an inpatient, monitored setting under medical supervision and immediate access to resuscitative measures. Infusion reactions observed in prior and ongoing studies have had their onset during the infusion itself.

Whether or not patients have been discharged from the hospital, they will undergo the Study Day 3 and Follow-up Day 30 visits to assess safety. Due to the theoretical possibility of antibody formation to andexanet, FX, FXa, or HCPs, antibody testing will be performed at baseline and at the Study Day 30 visit.

The independent EAC, in addition to adjudicating the primary endpoint, will also adjudicate all TEs, deaths, and all post-surgical bleeding events using pre-defined criteria as described in their charter. A DSMB will review all safety data on a schedule described in the DSMB charter.

In addition, safety data will be reviewed by the Sponsor at an ongoing basis.

Guidelines for the management of specific AEs are provided in Section 8.0.

3.6. Benefit and Risk Assessment

Factor Xa inhibitors are a significant therapeutic advance in several indications. However, a significant risk of anticoagulation with FXa inhibitors is the potential for uncontrolled bleeding. While andexanet is approved for the management of acute major bleeding related to FXa inhibitor use, it is unknown whether it is efficacious and safe in patients who require urgent surgery in the setting of recent use of an FXa inhibitor. Andexanet may be beneficial in reversing anticoagulation and, thus, facilitating normal hemostasis during the surgical procedure. In addition to any personal benefit to individual patients, there is a potential benefit to all current and future patients treated with andexanet (and, more generally, all patients taking FXa inhibitors) from the insights gained through this clinical study. The risks of study participation involve the risk of experiencing an AE related to andexanet or to the study procedures. To date, no major safety issues directly attributable to andexanet have definitively emerged in clinical studies. However, whenever chronic anticoagulation is reversed in patients with an indication to receive it, the risk of thromboembolic events is increased. Additionally, surgical intervention can also increase thromboembolic risk. This risk must be balanced against the potential for new or worsening bleeding related to the surgery. The PD effect of andexanet is short. Therefore, shortly after the infusion is discontinued and once the potential for bleeding is minimized, it will be possible to return the patient to a therapeutically anticoagulated state as needed. It is recommended that the Investigator carefully weigh the risk of new bleeding against the risk of thrombosis when considering when to resume anticoagulation for the patient.

The safety monitoring plan for this study is robust (see Section 3.5), including treatment of patients in a hospital setting, an approximate 30-day safety follow-up, ongoing review of safety data by the Sponsor and independent safety reviews by the DSMB as well as adjudication of TEs and post-surgical bleeding events by the EAC.

Based on the above considerations, the potential risks to patients in this study are justifiable. Patients or their legally authorized representative will be consented as to the potential risks and will be required to sign an informed consent form (ICF), documenting their understanding of these risks and willingness to participate in the study.

4.0 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1. Inclusion Criteria

All of the following criteria must be met for the patient to be eligible to participate in the study:

1. Either the patient or his or her medical proxy (or legal designee) has given written informed consent prior to Screening.
2. Age ≥ 18 and < 85.
3. Requires urgent surgical intervention that must occur within 12 hours of clinical presentation, for which reversal of anti-fXa activity is judged necessary.
4. Received 1 of the following FXa inhibitors within 15 hours prior to start of surgery: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d), OR if a local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL (> 0.5 IU/mL for enoxaparin), the patient may be enrolled, irrespective of the time of the last dose.
5. Have a negative pregnancy test documented prior to enrollment (for women of childbearing potential).
6. Willingness to use medically acceptable methods of contraception through 30 days following study drug dose (for female and male patients who are fertile).

4.2. Exclusion Criteria

If a patient meets any of the following criteria, he or she is *not* eligible to participate:

1. Surgery predicted to last > 4 hours or for which the risk of clinically meaningful uncontrolled or unmanageable bleeding is low.
2. Acute life-threatening bleeding at the time of Screening.
3. Any surgical procedure requiring cardiopulmonary bypass, an intra-aortic catheter, or the intra-operative use of systemic, intravascular, unfractionated heparin.
4. Expected survival of < 1 month due to comorbidity.
5. Existing “Do Not Resuscitate” order or similar advanced directive.
6. The patient has a recent history (within 30 days prior to Screening) of a diagnosed TE as follows: VTE (including DVT, PE, intracardiac thrombus); myocardial infarction (including asymptomatic troponin elevations); disseminated intravascular coagulation (DIC); acute traumatic coagulopathy; cerebrovascular accident; transient ischemic attack; unstable angina pectoris hospitalization; or severe peripheral vascular disease (see Appendix B for DIC scoring algorithm).
7. Acute decompensated heart failure or cardiogenic shock at the time of screening (see Appendix C for cardiogenic shock definition)

8. The patient has severe sepsis or septic or hemorrhagic shock at the time of Screening (see definition in Appendix C).
9. The patient is pregnant or a lactating female.
10. The patient has received any of the following drugs or blood products within 7 days of enrollment:
    - VKA (e.g., warfarin).
    - Dabigatran.
    - Prothrombin complex concentrate products (PCC, e.g., Kcentra®), recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®).
    - Whole blood, plasma fractions.
    - Note: Administration of tranexamic acid (TXA), platelets, or packed red blood cells (PRBCs) is not an exclusion criterion.
11. The patient was treated with an investigational drug < 30 days prior to Screening.
12. Prior treatment with andexanet.

4.3. Criteria for Discontinuation from the Study

A patient may elect to discontinue participation in the study at any time. However, all efforts must be made to follow patients for the full duration of the study and to encourage all patients to complete the Day 30 contact.

This study will be conducted in such a way as to minimize patients that withdraw consent. The following points will apply:

- Patients who discontinue study treatment or some procedures should not be discontinued from the study. Investigators must distinguish the difference between patients who discontinue study drug or procedures from those who withdraw consent and do not intend to participate further in the study follow-up visits or contacts (withdrawers).
- The informed consent process will clearly alert patients to the negative effect that failure to complete the study has on its credibility.
- All Investigators must commit to minimizing the number of patients who do not complete the study.
- If patients cannot or will not return for visits, the Investigator (or their designee) should attempt to contact them by telephone or other means.

Reasons for all study withdrawals will be recorded.

4.4. Criteria for Discontinuation of Andexanet

Andexanet may be prematurely discontinued for a number of reasons, including:

- Any intolerable AE that cannot be ameliorated by appropriate medical intervention or that in the opinion of the Medical Monitor or Investigator would lead to undue risk if the patient were to continue on treatment.

Patients who discontinue study drug may still continue in the study. Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, in which case they should undergo an Early Termination visit.

Reasons for all discontinuations of andexanet will be recorded.

4.5. Patient Replacement

Patients who discontinue prematurely will not be replaced.

4.6. Study Completion

Study completion for each patient is defined as completion of the Day 30 visit or, at a minimum, the time at which Day 30 mortality data are recorded.

In certain European Union Member States, "study completion" may also be considered the same as "end of trial."

5.0 ENROLLMENT AND STUDY PROCEDURES

A summary of the patient visits and clinical evaluations can be found in Appendix A. Details on efficacy and safety assessments can be found in Section 10.0. Laboratory assessments or procedures performed per standard of care at presentation, but before signing of informed consent, may be used to assess eligibility.

5.1. Screening Period

5.1.1. Subject Identification Numbers

Patients will be considered to be in Screening once they have signed the ICF. At this time, patients will be assigned a patient identification number. Patients will be considered to have enrolled in the study once they have met the inclusion and exclusion criteria.

5.2. Visit Procedures (Days 1 to 30–37)

The visit procedures are described in the Schedule of Activities (Appendix A).

5.3. Unscheduled Visit

During the study, additional clinical visits may be scheduled at the Investigator's discretion in order to follow or evaluate AEs. The reason for an unscheduled visit will be recorded.

The following must be performed at an unscheduled visit:

- Record the reason for the unscheduled visit.
- Record AEs since last study visit.
- Record use of concomitant medication since last study visit.

Additional procedures may be performed at an unscheduled visit as deemed necessary by the Investigator. These may include any of the central or local laboratory testing done at scheduled visits, vital signs, additional evaluations for bleeding, or assessment of AEs.

5.4. Early Termination Visit

An Early Termination visit will be conducted if the patient discontinues from the study before the Follow-up Day 30 visit. Procedures at this visit will include the following:

- Record the reason for early termination.
- Record AEs since last study visit.
- Record use of concomitant medication since last study visit.
- Record dates of use of anticoagulant(s) on the anticoagulant CRF.
- Perform a final assessment of bleeding.

- Collect central laboratory specimens for TG and antibodies (anti-andexanet, anti-fX, anti-fXa, anti-HCP, and nAbs).

Vital signs and local laboratory assessments for complete blood count (CBC) and chemistry should also be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.

6.0 DRUG SUPPLIES AND DOSING

6.1. Formulation

Andexanet alfa (PRT064445) for Injection is supplied as a 200 mg/vial by Portola Pharmaceuticals, Inc. as a lyophilized product for reconstitution for IV injection. It is supplied in single-use, type I glass vials with grey rubber stoppers and flip-off seals. The filled vials contain 200 mg of andexanet (at 10 mg/mL after reconstitution). The composition in each vial is listed in Table 1. The lyophilized product must be reconstituted using Sterile Water for Injection before use. For details on reconstituting/ preparing andexanet, please refer to the Pharmacy Manual.

Table 1: Reconstitution Volumes and Composition for Andexanet for Injection

Vial Contents	**200 mg Vial**
Reconstitution Volume	**20.0 mL WFI**
Ingredients	***Quantity per Vial***
Andexanet (PRT064445)	200 mg
Tris (Tromethamine)	6.52 mg
Tris HCl	7.33 mg
L-Arginine Hydrochloride	94.8 mg
Sucrose	200 mg
Mannitol	500 mg
Polysorbate 80	2.0 mg
Sterile Water for Injection	QS to 20 mL (removed during lyophilization process)

QS = Quantity sufficient; WFI = Water for injection

6.2. Dosing and Administration

The initial andexanet dosing regimen will consist of an IV bolus, immediately followed by an IV continuous infusion lasting for 2 hours, irrespective of the duration of surgery. The start of the bolus will occur prior to, but not more than 30 minutes before, the start of surgery (i.e., at the first incision). It is possible that the bolus or infusion may be ongoing at the start of surgery. There are 2 possible dosing regimens (Table 2).

If the initial andexanet dosing regimen (bolus plus continuous infusion; ~2.5 hours) is completed prior to the end of the procedure, the infusion should continue at a low dose (4 mg/min) through the end of the surgery and the immediate post-operative period. To facilitate the extended infusion, approximately 30 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation. The total length of the initial course of andexanet (initial bolus/infusion plus extended infusion) should last no longer than 6 hours.

If a post-operative patient meets the applicable criteria for andexanet re-dosing (Table 2), he/she may be re-dosed. All patients that are re-dosed will be administered a low-dose bolus (400 mg) plus continuous infusion (4 mg/min for 120 minutes). If a patient is re-dosed, a baseline anti-fXa activity sample will be drawn beforehand; no post-initiation anti-fXa activity will be obtained.

Table 2: Andexanet Dosing Paradigm and Criteria for Extended Treatment or Re-Dosing

Dose	Timing of Last Dose of FXa Inhibitor	Initial IV Bolus *	Follow-On IV Infusion *
Low Dose	**≥ 8 hours** OR **< 8 hours for** • Rivaroxaban ≤ 10 mg • Apixaban ≤ 5 mg • Enoxaparin ≤ 40 mg	400 mg at a target rate of 30 mg/min	4 mg/min for at least 120 minutes irrespective of the duration of surgery (extended treatment for longer surgeries)
High Dose	**< 8 hours** • Rivaroxaban > 10 mg; • Apixaban > 5 mg • Enoxaparin > 40 mg • Edoxaban 60 mg OR Dose or Time Unknown	800 mg at a target rate of 30 mg/min	8 mg/min for at least 120 minutes irrespective of the duration of surgery (extended treatment for longer surgeries)
Criteria for Re-Dosing with Andexanet			
Consider re-dosing with andexanet (400 mg bolus + 4 mg/min infusion) only if: a. New, clinically significant, surgery-related, post-operative bleeding occurs after initial course of andexanet (primary bolus + infusion and extended dosing, as applicable) is completed, AND b. The treating physician has clinical suspicion that the patient still has levels of FXa inhibition sufficient to contribute to the bleeding, AND c. Re-dosing initiation occurs within 12 hours after the start of the first course of andexanet treatment.		

6.3. Storage

The labeled storage condition for andexanet is refrigerated, (i.e., 2-8°C). The temperature of the medicine refrigerator should be monitored with an electronic temperature monitoring device.

6.4. Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write at least the date dispensed, dose dispensed, lot or batch code, person dispensing, and the patient's identification number on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record.

All partially used or unused drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to Portola Pharmaceuticals, Inc. or its designee only after written authorization is obtained from Portola or its designees. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 13.5.

7.0 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1. Prior Medications and Treatments

See Section 4.1 and Section 4.2 for restrictions on prior medications and treatments.

7.2. Concomitant Medications, Hemostatic, and Procoagulant Treatments

7.2.1. Anticoagulants and Antiplatelet Drugs

Investigators may choose to re-start anticoagulants or antiplatelet drugs (including, but not limited to prasugrel, ticagrelor, clopidogrel, aspirin, and non-steroidal anti-inflammatory drugs) at any time based on clinical judgment. If anticoagulants or antiplatelet agents are restarted during the study, the date, time, dose, and agent(s) used should be recorded on the CRFs. Heparin-based products deemed to be necessary per the Investigator's judgement (such as for postoperative DVT prophylaxis) may be started at any time. However, it should be noted that any agent with anti-fXa properties may be suboptimally effective when administered within 1 hour after cessation of andexanet infusion, as this time interval represents the effective $t_{½}$ of the drug.

7.2.2. Blood Products

To maintain uniformity in transfusion practices across study participants, it is strongly suggested that the trigger for PRBC transfusion is hemoglobin ≤ 8.0 g/dL (± 1 g/dL). The hemoglobin triggering a transfusion, clinical stability factors (e.g., shock) influencing the decision to transfuse, as well as the number of units transfused should be recorded on the CRFs.

Whole blood and platelet transfusions may be administered according to standard institutional/local practices and/or guidelines. Investigators may consider using pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, fresh frozen plasma [FFP]) per their judgement in case of hemodynamic necessity. Otherwise, treatment with the above products is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of procoagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP) and whole blood intraoperatively or within 12 hours following surgery will result in the patient being considered having poor hemostatic efficacy (see Table 3) with andexanet.

Use of blood products, including number of units transfused and the date and time of administration should be recorded on the CRFs.

7.2.3. Hemostatic Agents

Investigators may consider using systemic anti-fibrinolytic (e.g., aminocaproic acid and TXA) and other systemic hemostatic agents if a patient is found to require further hemodynamic support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Similarly, local hemostatic agents (e.g., microfibrillar collagen and chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) may be used if a patient is found to require further hemodynamic support. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Use of hemostatic agents, their dose, and the date and time of administration should be recorded on the CRFs.

7.3. Rescue Therapy

In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated for patients, due to post-surgical bleeding events. Investigators will therefore be allowed to deliver a second dose of andexanet as rescue therapy should such a situation arise. If rescue re-dosing is deemed necessary, Investigators will be required to document in the CRF the clinical justification for why subjects require additional dosing of andexanet. Re-dosing procedures will mirror those required for the initial andexanet dosing. Please refer to Appendix A for the timing of extended infusion or re-dosing of andexanet in surgical patients. The decision criteria for re-dosing are outlined in Section 6.2.

In the event a patient continues or restarts bleeding even after re-dosing with andexanet (or does not meet the criteria for re-dosing), standard of care should be employed and appropriately captured on the CRFs.

8.0 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

8.1. Infusion Reactions

As described in Section 1.4.6, mild to moderate infusion reactions have been reported in healthy subjects treated with andexanet. These infusion reactions have generally resolved without interruption of the infusion or medical intervention. In the event that the Investigator determines that intervention is warranted, consideration may be given to slowing the infusion rate, or temporary interruption of the dose followed by re-starting the infusion at a slower infusion rate. Treatment with diphenhydramine may also be considered.

8.2. Thrombotic Events

Patients will be monitored carefully for signs and symptoms of TEs (i.e., strokes, transient ischemic attacks, myocardial infarctions (MIs), DVTs, PEs, arterial systemic embolisms) throughout the course of the study. Should a diagnosis of a TE be considered, it is expected that an appropriate evaluation will be performed (e.g., head computed tomography [CT]/magnetic resonance imaging [MRI], electrocardiogram [ECG]/cardiac enzymes, lower extremity ultrasound, pulmonary vascular imaging). Investigators are requested to consult the guidance listed in Appendix E when considering whether an event should be considered a TE and therefore be submitted for adjudication. All events submitted for adjudication will be formally considered a suspected TE. Both suspected TEs and TEs confirmed by adjudication will be monitored as safety endpoints.

9.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs, including SAEs and non-serious AESIs, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

9.1. Safety Parameters and Definitions

9.1.1. Adverse Events

According to the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a patient administered a pharmaceutical product, which may or may not have a causal relationship with the treatment.

An AE can be any of the following:

- Unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug-related.
- Any newly occurring event or exacerbation of previous condition (e.g., increase in severity or frequency) since the administration of study drug.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

9.1.2. Serious Adverse Events

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Is fatal (i.e., the AE actually causes or leads to death).
- Is life-threatening. Life-threatening means that, in the opinion of the Investigator or Study Sponsor, the patient/subject was at immediate risk of death from the reaction as it occurred, (i.e., it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in a neonate/infant born to a mother who was exposed to study drug or where the father was exposed to study drug before conception.
- Is an important medical event. An important medical event is an event that may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

A distinction should be made between the terms "serious" and "severe" since they **are not** synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on the strict regulatory definitions listed above and serves as a guide for defining regulatory reporting obligations. A severe AE does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE if the event does not meet the serious criteria. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild but would be defined as an SAE based on the above noted serious criteria. Thus, severity and seriousness need to be independently assessed for each AE recorded on the AE electronic Case Report Form (eCRF).

9.1.3. Non-Serious Adverse Events of Special Interest

The AESIs for this study include the following:

- A thrombotic or embolic event of any severity

All AESIs, whether serious or non-serious, must be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Non-serious AESIs must be entered on the AE eCRF with a check in the AESI box.

9.2. Methods and Timing for Capturing and Assessing Safety Parameters

The Investigator is responsible for ensuring that all AEs (Section 9.1.1 for definition) are recorded on the AE eCRF and reported to the Sponsor in accordance with instructions provided in this section.

For each AE recorded on the AE eCRF, the investigator will make an assessment of seriousness (Section 9.1.2), causality (Section 9.2.2), and severity (Section 9.2.3).

9.2.1. Adverse Event Reporting Period

To comply with regulatory requirements, all SAEs and non-serious AESIs, regardless of causality, that occur from the date of signing of the ICF until 30 days after the last study drug treatment, must be reported to Portola or its safety designee within 24 hours from Investigator awareness of the event. Survival status and reason for death will be ascertained at the Follow-up Day 30 study visit.

Subjects who experience an andexanet-related AE or SAE will be followed until the AE or SAE is resolved or until a new stable baseline is established, even if this occurs after the Follow-up Day 30 visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate CRF through the Follow-up Day 30 visit.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported to Portola or safety designee. These pre-dose AEs will be collected on the AE eCRF and assessed as not related to study drug, but will be assessed for relationship to study procedures/tests and interventions.

After initiation of study drug, all TEAEs, regardless of relationship to study drug, will be reported until **30 days after the last dose of study drug**. Any SAE that occurs with an onset date later than 30 days after completion of the study and that the Investigator considers to be related to study medication must be reported to Portola or safety designee.

To report any SAEs, the SAE Report Form provided to the clinical study site must be completed with the available information. Non-serious AEs that are AESIs must be reported on the SAE form with the box for AESI checked. The information collected must include at minimum the following: patient number, study drug(s) received, the event term, the serious criteria met for the AE, a narrative description of the event, and an assessment by the Investigator of the severity/intensity of the event and relationship to study drug(s). The SAE report should be sent to Portola or safety designee within 24 hours of Investigator awareness. Follow-up information on the SAE should be sent promptly by the Investigator to Portola or safety designee when any additional relevant information about the SAE becomes known to the Investigator, or as requested by Portola or safety designee. Safety reporting contact information is located in the Study Reference Manual.

Portola will immediately notify the Investigator about important safety or toxicology information, including antibodies against FX or FXa identified in a patient treated with andexanet in any clinical study, as it becomes available. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) about new and relevant safety information regarding the study drug, including serious adverse

drug reactions involving risk to human subjects, in accordance with the applicable policies. Certain countries (e.g., the Netherlands), require Portola to notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not listed by nature or severity in the Investigator's Brochure.

9.2.2. Assessment of Causal Relationship

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or re-introduction of study drug (as applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

The following categories should be used in the causality assessment of suspected adverse reactions:

Probable

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; and
- Was unlikely to have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Possible

The AE:

- Follows a reasonable temporal sequence from the time of study drug administration; and/or
- Follows a known response pattern to the study drug; but

- Could have been produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unlikely

The AE:

- Does not follow a reasonable temporal sequence from the time of study drug administration; and
- Was most likely produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy.

Unrelated

- This category is applicable to those AEs that are judged to be clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention other than bleeding control, or concomitant therapy) and do not meet the criteria for study drug relationship listed under Probable, Possible, or Unlikely.

An AE with causal relationship not initially determined will require follow-up to assign causality. Importantly, lack of efficacy does not necessarily constitute relatedness to study drug.

9.2.3. Assessment of Severity

The Investigator must determine the severity of the event according to the criteria below and the Investigator's clinical judgment. Severity describes the intensity of the AE.

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living
Grade 4	Life-threatening consequence or urgent intervention indicated
Grade 5	Event resulted in death

9.2.4. Procedures for Recording AEs

Investigators should use correct medical terminology/concepts when recording AEs on the AE eCRF. Avoid colloquialisms and abbreviations. Only 1 AE term should be recorded in the event field on the AE eCRF.

All AEs spontaneously reported by the patient and/or in response to an open-ended question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate forms in the eCRF.

Only 1 AE term should be recorded in the event field on the AE eCRF. When possible, a unifying diagnosis, or signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as a "common cold" rather than listing each symptom separately.

9.2.4.1. Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the AE eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases; record tumor lysis syndrome rather than hypocalcemia, hyperkalemia, hyperuricemia, etc.). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the AE eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

9.2.4.2. Adverse Events that are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the AE eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all 3 events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the AE eCRF if it is unclear as to whether the events are associated.

9.2.4.3. Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the AE eCRF with the severity (intensity or grade) of the events recorded at the time the event is first reported.

A recurrent AE is one that resolves between patient evaluation time points and subsequently recurs, or notes a change in severity or seriousness. Each recurrence of an AE should be recorded as a separate event on the AE eCRF. For example:

- If Grade 1 vomiting has worsened to Grade 2 five days after onset, the Grade 1 vomiting is resolved on the date when the severity changed, and Grade 2 vomiting is recorded as a new event on the eCRF with onset date reflecting the change in severity.

If non-serious event of neutropenia required hospitalization 5 days after onset, the event is resolved on the hospitalization date, and a new SAE of neutropenia is recorded on the eCRF with start date reflecting when the event required hospitalization

9.2.4.4. Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the AE eCRF.

9.2.4.5. Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Is clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the AE eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the AE eCRF (Section 9.2.4.3 provides details on recording persistent AEs).

9.2.4.6. Deaths

Death should be considered an outcome and not a distinct event. All deaths that occur during the protocol-defined AE period should be reported as SAEs, regardless of attribution to study drug. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept (e.g., septic shock) with a fatal outcome. When the event that led to death cannot be identified (e.g., death of unknown origin) report "unexplained death" as the adverse event AE and update it when new information clarifies the event that led to death. Only 1 AE can be reported with a fatal outcome for each patient who dies. Other AEs that continued up to time of death should be reported with an outcome of not recovered/resolved. In the event that the death is attributed solely to natural progression of the underlying bleeding, the event is not reportable and should not be recorded as an AE.

9.2.4.7. Preexisting Medical Conditions

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the AE form, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.2.4.8. Hospitalization or Prolonged Hospitalization

The following hospitalizations are not considered SAEs in this clinical trial:

- Admissions per protocol for a planned medical/surgical procedure. Planned hospital admissions or planned surgical procedures for an illness or disease that existed before the patient was enrolled in the trial or before study drug was given are not to be considered AEs, unless they occur at a time other than the planned date for a reason such as a worsening of the underlying disease/illness/symptoms.
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy).
- Medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases.

Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

9.2.4.9. Pregnancy Exposure and Birth Events Reporting

Andexanet is not expected to have reproductive or developmental toxicity based on the following:

- Andexanet is intended for single-dose administration and, therefore, has limited potential for reproductive or developmental toxicity.
- Andexanet is a biotechnology-derived protein that is a modification of an endogenous protein in the coagulation cascade (FXa).
- Andexanet has a very short $t_{½}$ (1–2 hour effective $t_{½}$).
- Andexanet was designed as a universal antidote for FXa inhibitors, which are prescribed primarily in elderly patient populations that are not of reproductive capacity.

However, it is recommended that women of childbearing potential must use 2 medically acceptable methods of contraception, at least 1 of which must be a barrier method (e.g., non-hormone containing intra-uterine device plus condom, spermicidal gel plus condom), through at least 1 month following study drug dose.

Additionally, men with sexual partners of childbearing potential must use 2 acceptable methods of contraception, at least 1 of which must be a barrier method (e.g., spermicidal gel plus condom), for the entire duration of the study and for at least 1 month following study-drug; and men must refrain from attempting to father a child or donating sperm in the month following the study-drug.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a female study patient becomes pregnant or a female partner of a male study patient suspects she is pregnant, the Investigator should be informed immediately. Portola must, in turn, also be notified by the Investigator immediately by completing a Pregnancy Form. If a female partner of a male study patient is pregnant or suspects she is pregnant, the male patient will be advised by the study Investigator to have his pregnant partner inform her treating physician immediately. The pregnancy must be followed up through delivery or other fetal outcome and information reported on a Pregnancy Follow-up form. For any abnormal fetal outcome (including congenital anomaly or birth defect, spontaneous or therapeutic abortion, still birth, pre-mature birth, or other outcome other than live normal birth), the Investigator should promptly report the abnormal fetal outcome to the Sponsor on an SAE form.

10.0 STUDY ASSESSMENTS

Details on the collection, processing, storage, and shipment of samples are contained in the Laboratory Manual.

10.1. Efficacy Assessments

Efficacy assessments that require collection and evaluation of laboratory samples are described in the subsections that follow; other efficacy assessments are described in Section 11.5.2.

10.1.1. Anti-fXa Activity

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

10.1.2. Thrombin Generation

Thrombin generation will be measured using plasma samples to assess the ability of andexanet to reverse the anticoagulant effect of FXa inhibitors. Thrombin generation will be measured using a tissue factor (TF)-initiated TG assay. This assay will be performed at a Central Laboratory. Five parameters related to TG are measured: endogenous thrombin potential (ETP), peak height, time to peak height, lag time and velocity index. Endogenous thrombin potential is prospectively identified as the primary measure for TG.

10.1.3. Tissue Factor Pathway Inhibitor

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

10.1.4. Anti-IIa Activity

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

10.1.5. Safety Assessments (other than Adverse Events)

10.1.5.1. Vital Signs

Vital signs include temperature, systolic blood pressure (SBP), diastolic blood pressure, heart rate, and respiratory rate.

10.1.5.2. Physical Examination

A focused physical examination will be performed on all patients at various time points (see Appendix A) before and after the surgical procedure. The examination will include, at a minimum, any component relevant to the indication for surgery (e.g., abdominal examination for appendicitis, hip examination for hip fracture, neurologic examination for spinal cord compression) and an assessment of the surgical incision site (post-operative only).

10.1.5.3. Antibody Testing

Determination of the possible presence of antibodies to FX (human) and FXa (human) will be done at specific time points (see Appendix A) using the modified Bethesda assay. Antibodies against andexanet and HCPs will assessed using standard immunogenicity assays.

For any sample that is positive for antibodies against andexanet, the potential for nAb activity will be further assessed by measuring the functional activity of andexanet in plasma. These tests will be performed by a Central Laboratory.

10.1.5.4. Clinical Laboratory Testing

Blood specimens for routine chemistry and hematology will be obtained at selected time points (see Appendix A).

The following assays will be performed at the Local Laboratory:

- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count, platelet count, WBC differential
- Coagulation: INR
- Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total, direct, and indirect bilirubin
- Serum or urine pregnancy test (in women of child bearing potential; see Appendix D)

10.1.5.5. Optional Local Laboratory Testing of Anti-fXa Levels

Local laboratories may perform tests to evaluate anti-fXa activity to address inclusion criterion 4. Further details and guidance on the conduct of local point-of-care anti-fXa assays can be found in the Laboratory Manual for ANNEXA-S. Investigators are discouraged from evaluating anti-fXa activity with local assays after the administration of andexanet, due to the known inaccuracy of post-andexanet results caused by the large sample dilutions associated with commercial anti-fXa assays; however, if such testing is deemed necessary, it is strongly recommended that the procedures outlined in the Laboratory Manual be followed.

11.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study objectives and study design are described in Sections 2.0 and 3.1, respectively. The information in this section is a summary of the planned statistical analyses. Further details will be provided in the detailed Statistical Analysis Plan.

11.1. General Considerations

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

All hypothesis tests will be 2-sided and reported at the 0.05 significance level. All confidence intervals (CIs) will be 2-sided and reported at the 95% confidence level.

11.2. Randomization

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

11.3. Analysis Populations

11.3.1. Enrolled Population

The enrolled population will consist of all patients enrolled (signed inform consent and met inclusion/exclusion criteria) into the study irrespective of whether they received andexanet or not.

11.3.2. Safety Analysis Population

The safety analysis population will consist of all patients enrolled and treated with any amount of andexanet.

11.3.3. Efficacy Analysis Population

The efficacy analysis population will include all enrolled patients who receive any amount of andexanet treatment and undergo surgery.

11.4. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized for all populations listed above. Data will be summarized using descriptive statistics of frequencies for categorical data and means, medians, standard deviations, minimums, and maximums for continuous data. No inferential analyses of these data are planned.

11.5. Efficacy Endpoints and Analyses

11.5.1. Definitions

Hemostasis will be assessed from the start of infusion to the end of the procedure. Categories for the assessment of effective hemostasis are provided in Table 3.

Table 3: Effective Hemostasis Categories

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

* Tranexamic acid excluded.

The evaluation period for anti-fXa activity covers the period of time from 5 minutes following the end of the andexanet bolus to just prior to the end of the andexanet infusion. The baseline measurement will be the last value obtained prior to andexanet treatment.

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

11.5.2. Efficacy Endpoints

11.5.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the achievement of hemostatic efficacy, as determined by the surgeon's assessment of intra-operative hemostasis and confirmed by adjudication by an independent EAC.

For each patient, hemostasis will be judged effective if effective hemostasis category is Excellent or Good, and ineffective if effective hemostasis category is Moderate or Poor.

A patient will be deemed non-evaluable if s/he meets the criteria specified in the EAC Charter.

11.5.2.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is the percent change in anti-fXa activity from baseline to the evaluation period nadir. The evaluation period starts 5 minutes after the end of the andexanet bolus and ends just prior to the end of the andexanet infusion.

Patients who do not have at least 1 anti-fXa activity level within the evaluation period will have percent decrease imputed as 0.0% (i.e., using the baseline value as the nadir value).

11.5.2.3. Exploratory Efficacy Endpoints

The following efficacy endpoints will be analyzed as exploratory:

- Anti-fXa activity as measured by additional parameters, including, but not limited to: on-treatment nadir, absolute change from baseline to on-treatment nadir, 12-hour nadir, number of patients with percent reduction from baseline > 80%.
- Reversal of anticoagulant effect as measured by TG parameters (with ETP as the primary measure).
- Occurrence of receiving 1 or more RBC transfusions from start of the andexanet bolus through 12 hours after the start of surgery.
- The number of RBC units transfused per patient from the start of the andexanet bolus through 12 hours after the start of surgery.
- The use of non-RBC, non-platelet blood products and/or hemostatic agents (both systemic and topical) through 12 hours after the start of surgery.
- Transfusion-corrected change in hemoglobin from baseline to nadir within 12 hours after the start of surgery.
- Time from the signing of informed consent to the start of surgery.
- Length of index hospitalization, assessed at the Day 30 visit.
- Time hospitalized in an ICU, assessed at the Day 30 visit.
- Length of surgery.
- Occurrence of re-hospitalization, within 30 days of enrollment, including length of re-hospitalization (through 30 days post enrollment).
- Occurrence of post-surgical bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery.
- Occurrence of re-operations for bleeding, including surgical wound hematomas, within 12 hours after the start of the initial surgery.
- Change from baseline in TFPI activity post-administration of andexanet.
- Change from baseline in anti-IIa activity (only patients taking enoxaparin).

11.5.3. Statistical Methodology for Endpoint Analyses

All efficacy analyses will be performed on the efficacy analysis population. All hypothesis tests and CIs will be 2-sided with α=0.05.

The primary endpoint, the proportion of patients who have effective hemostasis, will be summarized with a 95% CI. The null and alternative hypotheses tested to support this analysis are:

H_0: $\pi = 0.67$

H_1: $\pi \neq 0.67$

The study will be considered to have met its primary efficacy objective if the proportion of patients with effective hemostasis is statistically significantly higher than 67% ($p < 0.05$) using a 2-sided Chi-Square test with $\alpha = 0.05$, or the lower bound of the 2-sided 95% CI is greater than 0.67.

The secondary endpoint, percent change from baseline in anti-fXa activity from baseline to the nadir for the evaluation period, will be assessed with a 2-sided 95% nonparametric CI for the median. If the lower limit of the nonparametric CI for the median exceeds 0, the corresponding objective will be considered to have been met.

For the exploratory endpoints, counts data will be summarized by observed rates and associated 95% CIs. Continuous endpoints will be summarized by means or medians and associated 95% CIs.

11.6. Determination of Sample Size

A total sample size of approximately 200 patients is planned.

It is estimated that a sample size of 180 patients will provide approximately 89% power to reject the null hypothesis that 67% of the patients will achieve effective hemostasis. This power calculation assumes the true rate of achieving effective hemostasis is 77%. An approximate 10% attrition rate is expected (e.g., canceled surgeries, discontinued and/or non-evaluable patients). Therefore, 200 patients will be enrolled.

The expected rate of effective hemostasis in the andexanet population is based on interim efficacy results from ANNEXA-4, where the lower bound of the 95% CI for the achievement of hemostatic efficacy was 77% [4].

The sample size and power computations were performed using the software package PASS (Version 15, NCSS, LLC, Kaysville, Utah, USA).

11.7. Safety Endpoints and Summaries

Safety will be assessed by examining the following endpoints:

- AEs (including SAEs), vital signs, physical examinations, and clinical laboratory measurements.
- TEs within 30 days of enrollment, including those suspected and confirmed by adjudication.
- Centrally-adjudicated deaths within 30 days of enrollment, including all-cause mortality and cardiovascular mortality.
- Antibodies to FX, FXa, andexanet, and HCPs.

11.7.1. Adverse Events

Treatment-emergent adverse events, including preferred terms defined by the Medical Dictionary for Regulatory Activities (MedDRA), will be summarized by system organ class. Arterial and venous thromboembolic events, considered AESIs, will be summarized separately.

The number of events, the number of patients, and the percentage of patients who experienced at least 1 TEAE will be presented. The TEAEs that are considered by the Investigator to be related to the andexanet, TEAEs that lead to early withdrawals, and serious TEAEs will be summarized in the same manner. Frequent TEAEs, including preferred terms with an incidence rate of ≥ 5%, will also be summarized.

All potential post-surgical bleeding events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event.

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

11.7.2. Thrombotic Events

All TEs will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to the event.

11.7.3. Deaths

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

11.7.4. Laboratory Parameters

Clinical laboratory parameters performed at the Central Laboratory (e.g., anti-fXa activity and TG) will be summarized by time point. For patients with anti-fXa activity levels obtained locally by a point-of-care assay, values will be documented but not formally analyzed.

Baseline values, the values at each subsequent visit, and changes from baseline will be summarized for each of the quantitative laboratory assessments.

11.7.5. Vital Signs

Vital signs will be summarized using actual values and change from baseline at pre-specified time points for each treatment group. Descriptive statistics, including threshold-based outlier analyses, will be presented.

11.7.6. Physical Examinations

Findings on physical examination will be summarized in a listing.

11.7.7. Antibodies

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

11.8. Interim Analyses

There is 1 formal interim analysis planned for this study when 50 patients complete the study. This analysis is planned to support the submission for accelerated approval. No adjustment to the type I error rate or CI coverage will be made to account for the interim analysis.

Following the formal interim analysis, interim summaries of safety data will be performed periodically at a minimum frequency of every 6 months in order to report safety data from the ongoing study. The DSMB will meet regularly to review the accumulating safety data.

11.9. Subgroup Analyses

Consistency of efficacy across important subgroups will be investigated within each cohort. At a minimum, primary efficacy will be summarized for subgroups of sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, and baseline anti-fXa activity (above and below threshold cutoffs of 30 ng/mL, 50 ng/mL, and 75 ng/mL).

12.0 STUDY COMMITTEES AND COMMUNICATIONS

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

- **Independent EAC**: Adjudication of hemostatic efficacy, deaths, TEs, and post-surgical bleeding events for all patients. The EAC will be blinded to all anti-fXa levels.
- **Independent DSMB**: Monitoring of all safety data.

13.0 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1. Institutional Review Board or Independent Ethics Committee

The protocol and ICF for this study must be reviewed and approved by an appropriate IRB or IEC before patients are enrolled in the study. It is the responsibility of the Investigator to assure that the study is conducted in accordance with current country and Local Regulations, ICH, GCP, and the Declaration of Helsinki. A letter, documenting the approval that specifically identifies the protocol by number and title as well as the Investigator, must be received by Portola Pharmaceuticals, Inc. before initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

After the completion or termination of the study, the Investigator will submit a report to the IRB or IEC, and to Portola Pharmaceuticals, Inc.

13.2. Informed Consent

Each patient must be provided with oral and written information describing the nature and duration of the study, and the patient must sign a written ICF in a language in which he/she is fluent before study-specific procedures are conducted. The signed and dated ICF will be retained with the study records. Each patient will also be given a copy of his/her signed ICF. Due to the critical nature of the illness under study and the possibility that patients will be unable to provide their own consent, proxy consents (defined as consent from a legally authorized representative) and/or emergency consents (defined as consent from a qualified medical professional) are allowed if permissible by local or regional laws and regulations.

13.3. Documentation

The Investigator must provide Portola Pharmaceuticals, Inc. with the following documents (copies of which must be maintained by the Investigator):

1. Curriculum vitae of the Investigator and any sub-investigators listed on the Form FDA 1572.
2. A signed copy of the IRB or IEC approval notice for protocol and informed consent.
3. A copy of the IRB- or IEC-approved ICF.
4. Laboratory certification with a list of normal values for laboratory tests that will be conducted at local laboratories.
5. Completed financial disclosure form for the Investigator and any sub-investigators listed on the Form FDA 1572.

13.4. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic Case Report Form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 Code of Federal Regulations (CFR) Part 11-compliant Electronic Data Capture (EDC) system, as appropriate. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Some clinical laboratory data will be collected externally from the EDC systems. Further details for data collection and data handling will be specified in the data management plan, CRFs, instructions for completing forms, other data handling procedures, and procedures for data monitoring. The MedDRA coding dictionary will be used for coding AEs, medical history conditions, and procedures. The reconciliation of the SAEs between the clinical and safety databases will be conducted as specified in plans determined and approved prior to study start-up. The WHO-DD dictionary will be used to code medications.

13.5. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

13.6. Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify the Portola Pharmaceuticals Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Deviations due to non-compliance that render subject non-evaluable for key endpoints will be considered significant deviations. Any other changes in the protocol will be made as an amendment to the protocol and must be approved by Portola Pharmaceuticals, Inc. and the IRB or IEC — before the changes or deviations are implemented.

Portola Pharmaceuticals, Inc. will not assume any responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol.

13.7. Disclosure of Data

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Patient confidentiality will be further assured by utilizing patient identification code numbers to correspond to treatment data in the computer files. The study personnel, employees of the regulatory agencies, including the US FDA and the study sponsor, Portola Pharmaceuticals, Inc., and its agents will need to review patient medical records in order to accurately record information for this study. If results of this study are reported in medical journals or at meetings, the patient's identity will remain confidential.

13.8. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates andexanet was received from Portola and prepared for the study, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site, in accordance with approved written procedures, or returned to Portola Pharmaceuticals, Inc. after written authorization is obtained from Portola Clinical Development. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Portola. All records will be retained as noted in Section 13.5.

13.9. Study Monitoring

The Investigator will allow representatives of Portola Pharmaceuticals, Inc. to periodically review (at mutually convenient times before, during, and after the study has been completed) all CRFs and relevant portions of office, clinical, and laboratory records for each patient. Appropriate source documents, including documents that support patients' eligibility (e.g., medical history, concomitant medications) should be made available to the study monitor. The monitoring visits provide Portola Pharmaceuticals, Inc. with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

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15.0 LIST OF APPENDICES

APPENDIX A. SCHEDULE OF ACTIVITIES

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	1								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Obtain Consent	X										
Determine Eligibility	X										
Obtain Medical History	X										
Obtain Prior Medications and Time of Last Anticoagulant Dose or Plasma Level	X										
Obtain ASA Class			X								
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X	X	X			
Weight (actual reported/recent)	X										
Physical Examination	X							X	X	X	X
Central Labs: Anti-fXa and anti-IIa Activity		X			X		X	X			
Central Labs: Thrombin Generation	X	X			X		X	X	X	X	
Central Labs: Antibodies to andexanet, HCPs, and FX/FXa (modified Bethesda); and nAb (andexanet)	X										X

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	1								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Central Labs: TFPI activity		X					X	X	X	X	X
Local Labs: PT-INR	X										
Local Labs: Chemistry and Pregnancy Test [3]	X										
Local Labs: CBC		X					X	X			X
Prepare andexanet (all patients)	X										
Administer andexanet Bolus, Immediately Followed by an Infusion			**Bolus + Infusion**								
Assess Need for Extended Andexanet Infusion.(if Surgery Ongoing)						X [4]					
Surgical Intervention				SURGERY							
Record Blood Loss Post Surgery							X				
Record Investigator Assessment of Intra-operative Hemostasis							X				
Record Blood Products & Hemostatic Treatments [5]		X									
Record Bleeding-Related Diagnostic & Therapeutic Procedures [6]		X							X	X	

	Screening & Baseline		Treatment						Follow-Up		
STUDY DAY:	**1**								**2**	**3**	**30 or ET**
TIME POINT AND WINDOW: All time points relative to start of surgery	**-2 hours to -45 min**	**-45 min to -30 min**	**-30 min to -5 min**	**Start of Surgery (SoS) [1]**	**SoS + 1 h** ± 15 min	**SoS + 2 h** ± 15 min	**EoS [2]** ± 15 min	**SoS + 12 h** ± 1 h	**SoS + 24 h** ± 1 h	**SoS + 72 h** ± 1 h	+ 7 days
Record Volume of Colloid and Crystalloid [5]		X									
Record Hours in ED, ICU/Critical Care, General Hospital Floor, and Total as an Inpatient											X
Record AEs	X	X							X	X	X
Record Concomitant Medications	X	X							X	X	X
Ascertain Survival Status											X

AE = Adverse event; ASA = American Society of Anesthesiologists; BP = Blood pressure; CBC = Complete blood count; CRF = Case report form; CT = Computed tomography; d = Day(s); ED = Emergency department; EoS = End of Surgery; ET = Early Termination; FX = Factor X; FXa = Activated factor X; h = Hour(s); HCP = Host cell protein; HR = Heart rate; ICU = Intensive care unit; INR = International normalized ratio; IV = Intravenous; min = Minute(s); nAb = Neutralizing antibody (activity); PT = Prothrombin time; RR = Respiratory rate; SoS = Start of Surgery; Temp = Temperature; TFPI = Tissue factor pathway inhibitor

[1] Start of surgery is Time 0 and must be within 15 hours of the last FXa inhibitor dose.

[2] The EoS time point may occur before SoS + 1 hour or SoS + 2 hour; EoS procedures should be carried out when EoS occurs.

[3] Pregnancy test in women of childbearing potential; test may be done on urine or serum.

[4] Approximately 30 minutes prior to the end of the andexanet infusion, the investigator should inform the pharmacy whether additional andexanet will be needed, to allow time for preparation.

[5] Colloid, crystalloid, hemostatic agents, and blood products administered prior to arrival in the ED should also be recorded.

[6] Record procedures performed to evaluate bleeding source/extent and for treatment of bleeding.

APPENDIX B. DISSEMINATED INTRAVASCULAR COAGULATION (DIC) SCORING ALGORITHM [6]

Note: Algorithm should only be used for patients with an underlying disorder known to be associated with overt DIC. A score of ≥ 5 is compatible with overt DIC.

Laboratory Test	Result	Score
Platelet Count	≥ 100 x 10^9 / L	0
	< 100 x 10^9 / L	1
	< 50 x 10^9 / L	2
D-Dimer, Fibrin Degradation Products	No increase	0
	Moderate increase	2
	Strong increase	3
Prothrombin Time	< 3 seconds	0
	≥ 3 but < 6 seconds	1
	≥ 6 seconds	2
Fibrinogen Level	≥ 1 g/L	0
	< 1 g/L	1

APPENDIX C. DEFINITIONS OF CARDIOGENIC SHOCK, SEVERE SEPSIS AND SEPTIC SHOCK [7]

Cardiogenic shock is a cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion [8]. The definition of cardiogenic shock may be clinically determined and consists of the following: Systolic blood pressure (SBP) < 90 mmHg for at least 30 minutes, OR

- Hemodynamic support required to maintain SBP ≥ 90 mmHg, AND
- End-organ hypoperfusion (e.g., urine output < 30 mL/hr or cool extremities)

Cardiogenic shock may also be optionally defined by hemodynamic criteria obtained through invasive hemodynamic monitoring:

- Cardiac index ≤ 2.2 L/min/m^2, AND
- Pulmonary capillary wedge pressure ≥ 15 mmHg

Severe sepsis is defined as sepsis-induced tissue hypoperfusion or organ dysfunction with any of the following thought to be due to the infection:

- Sepsis-induced hypotension
- Lactate above upper limit of normal (ULN)
- Urine output < 0.5 mL/kg/hr for more than 2 hours despite adequate fluid resuscitation
- Acute lung injury with partial pressure oxygen-arterial (PaO_2)/fraction of inspired oxygen (FIO_2) < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO2/FIO2 < 200 in the presence of pneumonia as infection source
- Creatinine > 2 mg/dL (176.8 micromol/L)
- Bilirubin > 4 mg/dL (34.2 micromol/L)
- Platelet count < 100,000 $microL^{-1}$
- Coagulopathy (International normalized ratio [INR] > 1.5)

Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.

Sepsis-induced hypotension is defined as a SBP < 90 mmHg, or mean arterial pressure (MAP) < 70 mmHg, or a SBP decrease > 40 mmHg, or less than 2 standard deviations below normal for age in the absence of other causes of hypotension.

Septic shock is defined as sepsis-induced hypotension (as defined above) persisting despite adequate fluid resuscitation.

APPENDIX D. DEFINITION OF FEMALE OF CHILDBEARING POTENTIAL

All women of childbearing potential (including those who have had a tubal ligation) will have a urine or serum pregnancy test at screening. If the pregnancy test is positive, andexanet should not be administered.

All female patients are considered to be of childbearing potential **unless** they meet 1 of the following criteria:

1. The patient has been post-menopausal (amenorrheic) for at least 1 year
2. The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to screening
3. The patient had a hysterectomy

APPENDIX E. GUIDANCE FOR SUBMISSION OF POTENTIAL THROMBOTIC EVENTS FOR ADJUDICATION

Adjudication criteria for the diagnosis transient ischemic attacks, strokes, myocardial infarctions, venous thromboembolism, and arterial systemic embolism are provided below.

Transient Ischemic Attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, with signs or symptoms lasting < 24 hours and no evidence of new infarct on neuroimaging if performed. Investigators should consider submitting cases for adjudication if an event meets this definition.

Stroke is defined as an acute episode of neurological dysfunction consistent with a vascular cause. A stroke will be considered to have occurred if there is a rapid onset of signs and/or symptoms of a new persistent neurological deficit consistent with an obstruction to cerebral blood flow with no apparent nonischemic cause (e.g., trauma, tumor, or infection). Signs or symptoms must last at least 24 hours or, for symptom onset less than 24 hours, have neuroimaging evidence of new infarct. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. For the diagnosis of stroke, the following criteria must be fulfilled:

- Rapid onset of a focal/global neurologic deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphagia/aphasia, hemianopia, amaurosis fugax, or other new neurological signs/symptoms consistent with stroke.
- The duration of a focal/global neurologic deficit is at least 24 hours, OR the neurological deficit results in death, OR there is neuroimaging evidence of a new infarct.
- There is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion).
- Confirmation of the diagnosis by at least 1 of the following: specialist evaluation, or brain imaging procedure (i.e., CT scan, MRI scan, cerebral vessel angiography).

If the acute neurological signs represent a worsening of a previous (baseline) deficit, the new signs must have either persisted for more than 1 week, or persisted for more than 24 hours and were accompanied by an appropriate new imaging finding.

Investigators should consider submitting cases for adjudication as a possible stroke if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., delirium, mental status changes) that are not otherwise explainable by an alternative etiology.

Since the adjudication of hemostatic efficacy encompasses changes in clinical neurologic function and hematoma volume, these findings will only be considered for thrombotic event adjudication if they clearly have an ischemic etiology.

Myocardial Infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis of MI:

- Detection of a risk and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the upper limit of normal (ULN) and with at least 1 of the following:
  - Symptoms of ischemia
  - New or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block
  - Development of pathological Q waves in the ECG
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
  - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before biomarkers were obtained, or before cardiac biomarker values would be increased
- Percutaneous Coronary Intervention (PCI) related MI is arbitrarily defined by elevation of cardiac Troponin (cTn) values (> 5x ULN) in patients with normal baseline values or a rise of cTn values> 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, (ii) new ischemic ECG changes, (iii) angiographic findings consistent with a procedural complication, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least 1 value above the ULN
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (> 10 × ULN) in patients with normal baseline cTn values. In addition, either (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Investigators should consider submitting cases for adjudication as a possible MI if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., angina, ventricular tachyarrhythmia, cardiogenic shock, heart failure) that are not otherwise explainable by an alternative etiology. All cases of unexplained sudden death should also be submitted for adjudication as a possible MI and/or PE.

Venous Thromboembolism is defined as a symptomatic DVT or PE confirmed by objective testing. Criteria for the objective confirmation of deep vein thrombosis include:

- A constant filling defect in 2 or more views on contrast venography in 1 or more proximal venous segments (iliac, common femoral, superficial femoral, popliteal)
- New or previously undocumented non-compressibility of 1 or more venous segments on compression ultrasound
- A clearly defined intraluminal filling defect on contrast enhanced computed tomography

Criteria for the objective confirmation of pulmonary embolism include:

- An intraluminal filling defect on pulmonary angiography
- Sudden contrast cut-off of 1 or more vessels more than 2.5 mm in diameter on a pulmonary angiogram
- A high probability VQ scan (1 or more segmental perfusion defects with corresponding normal ventilation)
- An abnormal non-high VQ scan plus criteria for the diagnosis of DVT
- An unequivocal, intra-arterial, un-enhancing filling defect in the central pulmonary vasculature (pulmonary trunk, main pulmonary arteries, anterior trunk, right and left interlobar and lobar arteries) on computed tomography

Investigators should consider submitting cases for adjudication as a possible VTE if they meet 1 or more of the above criteria, or have potential symptoms and/or conditions (e.g., lower extremity swelling, respiratory failure) that are not otherwise explainable by an alternate etiology. All cases of unexplained sudden death should also be submitted for adjudication as a possible PE and/or MI.

Arterial systemic embolism is defined as abrupt vascular insufficiency associated with clinical and other objective evidence of arterial occlusion in the absence of other likely mechanisms. Clinical signs and symptoms must be consistent with embolic arterial occlusion, and there must be clear evidence of abrupt occlusion of a systemic artery, with at least 1 type of supporting evidence, such as surgical report indicating evidence of arterial embolism, pathological specimens related to embolism removal, imaging evidence consistent with arterial embolism, or autopsy report. Investigators should consider submitting potential systemic arterial embolism cases for adjudication if they meet this definition.