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

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

DRUG NAME:	Andexanet Alfa
PROTOCOL NUMBER:	14-505
PHASE:	3b/4
TRIAL SPONSOR:	Portola Pharmaceuticals, Inc. 270 East Grand Avenue South San Francisco, CA 94080
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PROTOCOL DATE:	Original: 30-July-2014 Amendment 1: 30-January-2015 Amendment 2: 07-May-2015 Amendment 3: 27-October-2015 Amendment 4: 06-January-2017 Amendment 5: 02-July-2018 Amendment 6: 30-November-2018

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 have Acute Major Bleeding (ANNEXA-4)," and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 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 Have Acute Major Bleeding (ANNEXA-4)," and agree to abide by all provisions set forth therein.

I agree to comply with the ICH Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312, applicable Health Canada regulations/guidelines and all locally applicable laws.

PPD

30 Nov 2018
Date (DD Month YYYY)

Portola Pharmaceuticals, Inc.

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PROTOCOL SYNOPSIS

Title	Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor who have Acute Major Bleeding (ANNEXA-4)
Study Number	14-505
Study Phase	3b/4
Total Number of Centers	Up to 120 sites in North America, Europe, and Japan
Objectives	In FXa-inhibitor treated patients with acute major bleeding with reduced FXa activity, the objectives of this study are as follows: **Primary Efficacy Objectives:** • To demonstrate the decrease in anti-FXa activity following andexanet treatment. • To evaluate the hemostatic efficacy following andexanet treatment. **Secondary Efficacy Objective:** • To assess the relationship between decrease in anti-fXa activity and achievement of hemostatic efficacy in patients receiving a FXa inhibitor who have acute major bleeding and reduced FXa activity. **Exploratory Efficacy Objectives:** • For patients receiving apixaban, rivaroxaban, or edoxaban, to evaluate the decrease in the free fraction of the FXa inhibitor following andexanet treatment. • To evaluate the effect of andexanet on thrombin generation. • To evaluate the effect of andexanet on levels of Tissue Factor Pathway Inhibitor (TFPI). • To evaluate the effect of andexanet on levels of Antithrombin III (ATIII). • To evaluate the effect of andexanet on anti-factor IIa activity. • To evaluate hemostatic efficacy in ICH patients at high risk for hematoma expansion. • To evaluate the use of red blood cell transfusions. • To evaluate the use of other blood products and hemostatic agents. • To evaluate the occurrence of re-bleeding in patients following andexanet treatment. Re-bleeding is defined as follows: recurrent bleeding from the same anatomical site, or new bleeding from a different anatomic site within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. • For patients with ICH, to evaluate change in clinical status following andexanet treatment. **Safety Objectives:** • To evaluate the overall safety of andexanet including: adverse events, adjudicated thrombotic events (TEs) and deaths, vital signs, clinical laboratory measurements, and antibodies to FX, FXa, and andexanet. • To evaluate the 30-day all-cause mortality.

Study Design	This is a multicenter, prospective, open-label study of andexanet alfa (also referred to as "andexanet") in patients presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Attempts will be made to enroll patients on direct FXa inhibitors as well as those on indirect FXa inhibitors, and to limit the percentage of enrolled patients receiving indirect FXa inhibitors to ≤ 20%. A minimum of approximately 110 evaluable patients with ICH will be enrolled in the study. In order to achieve sufficient numbers of ICH patients, enrollment in other subgroups (e.g., patients with non-ICH bleeds) may be capped. Once the Informed Consent Form (ICF) is signed and eligibility is confirmed, patients with acute major bleeding will receive andexanet as an Intravenous (IV) bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. The start of the andexanet bolus must be within 18 hours following the last dose of FXa inhibitor, if the timing of the last dose is known. If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible—following the signing of the ICF and completion of pre-treatment procedures—but no later than 3 hours following the signing of the ICF. Patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received and the dose and timing of the most recent dose. For anti-fXa activity and diagnostic evaluations to support hemostatic efficacy (e.g., imaging tests, hemoglobin levels), baseline is defined as the most recent assessment prior to the start of the andexanet bolus. For post-baseline assessments, time 0 is defined as the end of the continuous andexanet infusion. Re-dosing may be administered when specific criteria are met. Patients will be evaluated for the primary hemostatic efficacy endpoints for 12 hours from the end of andexanet infusion with clinical and imaging assessments for bleeding: head Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), Glasgow Coma Scale (GCS), modified Rankin Score (mRS), and National Institutes of Health Stroke Score (NIHSS) (Appendix H) for Intracranial Hemorrhage (ICH); transfusion-corrected hemoglobin and hematocrit for non-visible bleeding; echocardiogram for pericardial bleed; and CT/MRI scan for intraspinal bleeding. Hemostatic efficacy will be adjudicated by an independent Endpoint Adjudication Committee (EAC). In addition, re-bleeding episodes will be adjudicated according to the following definition: recurrent bleeding from the same or another anatomical site, or new bleeding from a different anatomical site, in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. The independent EAC will adjudicate whether patients met inclusion criteria, hemostatic efficacy, as well as all re-bleeding events, deaths, potential TEs, and AEs of special interest. 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 Adverse Events (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.

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). • Treatment Period: < 1 day (Day 1). 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 [refer to Section 6.2]). Safety Evaluation Period including Follow-up Period (AEs, survival): 30 days (Day 1 to the Day 30 study visit).
Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Either the patient or his or her medical proxy (or legally acceptable designee) has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening. 2. The patient must be at least 18 years old at the time of Screening. 3. The patient must have an acute overt major bleeding episode requiring urgent reversal of anticoagulation. Acute major bleeding requiring urgent reversal of anticoagulation is defined by at least ONE of the following: • 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. • Acute overt bleeding associated with a fall in hemoglobin level by ≥ 2 g/dL, OR a Hgb ≤ 8 g/dL if no baseline Hgb is available. • Acute bleeding in a critical area or organ, such as intraspinal, pericardial, or intracranial. 4. The patient, for whom the bleeding is intracranial or intraspinal must have undergone a CT or MRI scan demonstrating the bleeding. 5. The patient received or is believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d). 6. For patients with ICH, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation.

Exclusion Criteria	If a patient meets any of the following criteria, he or she is not eligible: 1. The patient is scheduled to undergo surgery in less than 12 hours after end of andexanet infusion, with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes - see more examples in Appendix G). 2. A patient with ICH has any of the following: • Glasgow Coma Score < 7 • Estimated intracerebral hematoma volume > 60 cc as assessed by the CT or MRI 3. Patients with visible, musculoskeletal, or intra-articular bleeding as their qualifying bleed. 4. The patient has an expected survival of less than 1 month. 5. The patient has a recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) as follows: Venous Thromboembolism (VTE; e.g., deep vein thrombosis, pulmonary embolism, intracranial venous thrombosis), myocardial infarction (including an isolated troponin elevation), disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to screening (see Appendix E for DIC scoring algorithm). 6. The patient has severe sepsis or septic shock at the time of Screening (see definition Appendix F). 7. The patient is pregnant or a lactating female. 8. The patient has received any of the following drugs or blood products within 7 days or Screening: • Vitamin K Antagonist (VKA) (e.g., warfarin). • Dabigatran. • Prothrombin Complex Concentrate products (PCC, e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®). • Whole blood, plasma fractions. Note: Administration of platelets or packed red blood cells (PRBCs) is not an exclusion criterion. 9. The patient was treated with an investigational drug < 30 days prior to Screening. 10. Planned administration of PCC, Fresh Frozen Plasma (FFP), or rfVIIa from Screening until within 12 hours after the end of the andexanet infusion.

Test Product, Dose, and Mode of Administration

Andexanet will be administered as an IV bolus, immediately followed by a continuous infusion. There are two possible dosing regimens: a low dose (400 mg at a rate of 30 mg/min, followed by 480 mg at a rate 4 mg/min), and a high dose (800 mg at a rate of 30 mg/min, followed by 960 mg at a rate of 8 mg/min). Patients will receive a low or high dose according to the following table:

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose Before Andexanet Initiation	
		< 8 Hours or Unknown	**≥ 8 Hours**
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg/ Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg/ Unknown	High Dose	
Enoxaparin	≤ 40 mg	Low Dose	
	> 40 mg/ Unknown	High Dose	
Edoxaban	< 30 mg	Low Dose	
	≥ 30 mg/ Unknown	High Dose	
Unknown	Unknown	High Dose	

Criteria for Re-Treatment with Andexanet

Consider re-dosing with andexanet (bolus + infusion; dose adjusted per dosing table) only if:

a. Bleeding recurs at the same site, or occurs at a different anatomic site (as defined in Section 6.2) after initial andexanet bolus + infusion is completed, AND
b. Re-dosing initiation occurs within 24 hours after the end of the continuous andexanet infusion.

Efficacy Endpoints	**Primary Efficacy Endpoints** • The percent change from baseline in anti-fXa activity to the nadir during the evaluation period (where the evaluation period starts 5 minutes following the end of the andexanet bolus and ends 10 minutes after the end of the andexanet infusion), AND • The achievement of hemostatic efficacy. **Secondary Efficacy Endpoints** No additional endpoint is defined to support the secondary objective. **Exploratory Endpoints** • For patients receiving apixaban, rivaroxaban, or edoxaban to evaluate the decrease in free fraction of the FXa inhibitor following andexanet administration. • Andexanet reversal of anticoagulant effect as measured by Thrombin Generation (TG) parameters (with Endogenous Thrombin Potential [ETP] as the primary measure) for both the Tissue Factor (TF)-initiated assay and the non-TF-initiated assay. • TFPI levels (free and total) pre- and post-administration of andexanet. • ATIIII levels, pre- and post-administration of andexanet. • Anti-factor IIa levels, pre- and post-administration of andexanet. • The achievement of hemostatic efficacy in ICH patients at high risk for hematoma expansion. • The number of patients receiving one or more red blood cell transfusions from the start of the andexanet bolus through 12 hours after the end of andexanet infusion. • The number of red blood cell units transfused per patient from the start of the andexanet bolus through 12 hours after the end of the andexanet infusion. • The use of non-study-prescribed blood products and/or hemostatic agents. • The occurrence of re-bleeding following andexanet treatment. Re-bleeding is defined as follows: bleeding from the same or another anatomical site in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. • Change from baseline in GCS at 1 hour, 12 hours, and 30 days (for ICH patients only). • Change from baseline in mRS at 1 hour, 12 hours, and 30 days (for ICH patients only). • Change from baseline in NIHSS at 1 hour, 12 hours, and 30 days (for ICH patients only).

Safety Measurements	• AEs, vital signs, and clinical laboratory measurements. • Centrally-adjudicated TEs and deaths. • Antibodies to andexanet, FX, and FXa.
Sample Size	**Total Enrollment 500 Patients** A sample size of 162 efficacy evaluable patients will provide 80% power that the lower bound of a two-sided 95% CI for the primary efficacy variable of effective hemostasis is above 50%, demonstrating a response rate above 50% for that variable. This is based on an anticipated response rate of 61%. It is estimated that ~30% of the safety population will have anti-fXa activity < 75 ng/mL for patients receiving apixaban and rivaroxaban, < 40 ng/mL for patients receiving edoxaban, and < 0.25 IU/mL for patients receiving enoxaparin [1]; therefore these patients will not be included in the primary analysis. Additionally, it is estimated that up to 5% of patients will be non-evaluable for reasons unrelated to andexanet. Therefore, based on the current sample size calculation, it is anticipated that up to 250 patients may have to be treated to achieve the requisite number of evaluable patients. The sample size may be adjusted based on changes in enrollment strategy for various bleed types and FXa inhibitors, a need to meet regulatory requirements for sufficient numbers of patients for each FXa inhibitor and/or geographic region, or new information from registries, observational studies, clinical trials, and/or other sources. To accommodate a potential increase in sample size based on these factors, the total enrollment will be 500 patients.

Statistical Analysis Methods for Efficacy	The first primary efficacy endpoint – i.e., percent change in anti-fXa activity from baseline (last measurement before administration of andexanet) to nadir (the lowest level measured between 5 minutes prior to the start of andexanet administration and 10 minutes after the end of the andexanet administration) – will be calculated for each patient as change = 100 %×(post-baseline)/baseline. Percent change from baseline in anti-fXa activity will be assessed with two-sided 95% CIs. A nonparametric CI for the median will be reported. If the nonparametric CI for the median excludes 0, the first primary objective will be considered to have been met. The second primary efficacy endpoint – the proportion of patients who are adjudicated to have effective hemostasis (excellent or good) by the independent EAC – will be summarized as a point estimate with an asymptotic 95% confidence interval. The primary endpoints, including the specific comparators and the specific analysis sets for the second primary endpoint, will be ordered in a fixed sequence multiple comparisons (i.e., hierarchical) fashion. The assessment of the relationship between effective hemostasis and percent decrease in anti-fXa activity will use the following validation procedures. An analysis of Receiver Operator Characteristics (ROC) will be the primary tool used to assess the relationship. A test of change in anti-fXa activity (percent change from baseline) in patients who do and do not achieve effective hemostasis will be used to support the ROC graph. Two other analyses will also be presented: 1) Analysis of "Responders" (patients with a large percent decrease in anti-fXa activity) anchored to Hemostatic Efficacy. 2) Cumulative Distribution Function (CDF) Analysis. Counts data will be summarized by observed rates and exact 95% CIs. In addition, other analyses will be performed, allowing for adjustment of potentially confounding variables. Variables that may confound evaluation of a correlation between reversal of anti-fXa activity with effective hemostasis include anatomical location of bleeding, mechanism of injury (e.g., blunt vs. penetrating trauma; traumatic vs. spontaneous), severity of injury, severity of bleeding, presence and timing of interventions to stop bleeding (e.g., endoscopic cautery of bleeding ulcers, surgical ligation of bleeding vessel), and use of coagulation or hemostatic factors. Further details on the analysis methods for the efficacy endpoints will be provided in the Statistical Analysis Plan (SAP).
Statistical Analysis Methods for Safety	Safety will be assessed by examination of 30-day survival status, AEs (including central adjudication of TE events), vital signs, clinical laboratory measurements, thrombin generation, and antibodies to andexanet, FX, and FXa. These data will be descriptively summarized as described in Section 11.7 and in the SAP. Adjudicated TE and death events will be separately summarized.

LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse event
andexanet alfa	Recombinant factor Xa inhibitor antidote, PRT064445
ATIII	Antithrombin III
AUC	Area under the curve
BID	Twice a day
BP	Blood pressure
CBC	Complete blood count
CDF	Cumulative Distribution Function
CFR	Code of Federal Regulations
CI	Confidence Interval
$C_{max/min}$	Maximum/minimum observed concentration
CRF	Case report forms
CT	Computed tomography
D-dimer	Fibrin degradation product
DIC	disseminated intravascular coagulation
DSMB	Data Safety Monitoring Board
EAC	Endpoint Adjudication Committee
ED	Emergency department
EI	End of infusion
ETP	Endogenous thrombin potential
F1+2	Prothrombin fragment 1+2
FDA	Food and Drug Administration
FFP	Fresh frozen plasma
FX	Factor X
FXa	Factor Xa
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale/Score
GLP	Good Laboratory Practices
HR	Heart rate
ICF	Informed consent form
ICH	Intracranial hemorrhage, International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ISTH	International Society on Thrombosis and Haemostasis
IV	Intravenous

Term	Definition
LCMS	Liquid chromatography mass spectrometry
LMWH	Low molecular weight heparin
Mg	Milligram
Min	Minute
mL	Milliliter
MRI	Magnetic resonance imaging
mRs	Modified Rankin score
mRS	modified Rankin Score
nAb	Neutralizing antibody (activity)
Ng	Nanogram
NIHSS	National Institutes of Health Stroke Scale
PRBC	Packed red blood cell
PCC	Prothrombin complex concentrate
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Orally
PT	Prothrombin time
QD	Once daily
rfVIIa	Recombinant factor VIIa
ROC	Receiver Operating Curve
RR	Respiratory rate
RVVT	Russell's Viper Venom Time
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SEM	Standard error of the mean
SQ	Subcutaneously
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
VKA	Vitamin K antagonist
VTE	Venous thromboembolism

1.0 INTRODUCTION

1.1. Background

The class of Novel Oral Anticoagulants (NOACs) known as direct factor Xa (FXa) inhibitors has consistently demonstrated comparable or superior efficacy and/or safety relative to its predecessors, VKAs and Low Molecular Weight Heparins (LMWHs). In the United States, this new class of drugs is approved for the prevention of stroke in patients with non-valvular atrial fibrillation, the prevention of Venous Thromboembolism (VTE) in hip or knee replacement surgery, and the treatment and secondary prevention of Pulmonary Embolism (PE) and/or Deep Vein Thrombosis (DVT) [2, 3]. Despite their advantages over older standard therapies, the major concern regarding this new class of anticoagulants is the lack of an antidote to reverse anticoagulation in the setting of serious/life-threatening bleeding or urgent or emergency surgery. Prospective follow-up of 1,775 patients treated chronically with rivaroxaban for atrial fibrillation for stroke prevention or VTE disease, revealed that the bleeding rate in 100 patient-years was 59.4 events per 100 patient-years: 36.3 events per 100 patient-years were minor bleeding events as defined by the International Society on Thrombosis and Haemostasis (ISTH); 19.7 events per 100 patient-years were ISTH-defined non-major, clinically relevant bleeding events; and 3.4 events per 100 patient-years were ISTH-defined major bleeding events [4]. As the use of FXa inhibitor increases, the need to reverse acute major bleeding related to this class of drugs is expected to increase. Andexanet alfa is approved in the US as a reversal agent that is indicated for the treatment of patients with acute major bleeding while taking the FXa inhibitors apixaban and rivaroxaban.

It is known from experience with VKA-related bleeding that reversal of anticoagulation is associated with improved hemostatic efficacy [5] and reduced mortality [4]. International guidelines recommend that patients presenting with severe VKA-related bleeding be treated with reversal agents (prothrombin complex concentrate products [PCC] and Vitamin K) as soon as the diagnosis is confirmed. Use of guideline-recommended doses of PCC and Vitamin K within the first 8 hours is associated with a 50% decrease in 7-day mortality [4]. No agents are available, however, for reversing the anticoagulation related to direct FXa inhibitors. The clinical development of andexanet (coagulation factor Xa [recombinant], inactivated-zhzo) aims to fulfill this unmet medical need.

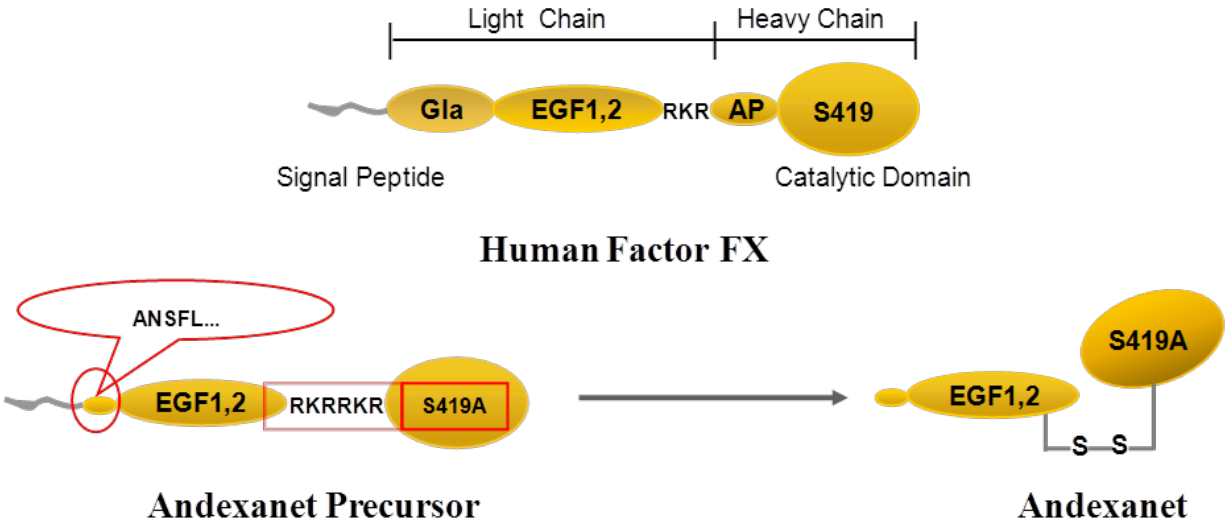
1.2. Description of Andexanet

Andexanet alfa has been specifically designed to neutralize the anticoagulant effect of direct and indirect FXa inhibitors. Andexanet is a modified FXa protein that has been truncated and inactivated so that it lacks physiologic blood coagulation factor activity but retains its high affinity for FXa inhibitors (Figure 1). The active site serine has been mutated to alanine, rendering the molecule unable to cleave and activate prothrombin. In addition, the membrane binding domain of plasma-derived FX has been deleted, rendering andexanet unable to assemble into the prothrombinase complex and thereby preventing an anticoagulant effect. Andexanet

binds to small molecule FXa inhibitors (e.g., apixaban [Eliquis®], edoxaban [Savaysa® or Lixiana®] and rivaroxaban [Xarelto®]) with a high affinity that is similar to native FXa. Due to this high affinity binding to FXa inhibitors, andexanet acts as a decoy molecule that is able to sequester the inhibitor, thereby rapidly reducing the free plasma concentration of the FXa inhibitor and neutralizing its anticoagulant effect. Andexanet also binds antithrombin III (ATIII) complexed with LMWH (e.g., enoxaparin [Lovenox® or Clexane®] or fondaparinux [Arixtra®]), similarly to endogenous FXa. In addition to reversal of anti-fXa activity, andexanet has been shown to reverse the anti-factor IIa activity of a low molecular weight heparin, enoxaparin, *in vitro*.

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

Figure 1: Structures of Human Factor X and Andexanet



1.3. Summary of Relevant Nonclinical Experience with Andexanet

1.3.1. Nonclinical Pharmacology

In vivo animal models have been used to demonstrate the correlation between reversal of anticoagulation as measured by pharmacokinetic (PK) and pharmacodynamic (PD) parameters (such as plasma unbound fraction of the anticoagulant, whole blood international normalized ratio (INR), anti-fXa activity) and reduction of blood loss in anticoagulated rodents [6, 7] and rabbits [8, 9].

Utilizing a rat tail transection model where animals were anticoagulated with supratherapeutic doses of enoxaparin, intravenous (IV) bolus administration of andexanet significantly reduced blood loss when given either prophylactically or after the initiation of bleeding. In these

experiments, administration of andexanet elicited a dose-dependent decrease in *ex vivo* plasma anti-fXa activity. In experiments where andexanet was prophylactically administered prior to tail transection, blood loss was reduced to levels seen in non-anticoagulated animals [10]. When andexanet was administered to bleeding animals, blood loss was reduced by a statistically significant 62% when anti-fXa activity was reduced by at least 35% [9]. These experiments demonstrated that reduction in blood loss correlated with a decrease in plasma anti-fXa activity and that restoration of hemostasis for a short period of time (i.e., minutes, due to the short half-life [$t_{½}$] of andexanet in rats) was sufficient to stop or significantly reduce blood loss in this model.

In a more clinically relevant *in vivo* model of visceral bleeding caused by liver laceration [11], andexanet was administered to rivaroxaban-anticoagulated rabbits either prophylactically or following tissue injury. In the prophylactic experiment, andexanet was compared to recombinant factor VIIa (rfVIIa, NovoSeven®) or 3-factor PCC (Bebulin®) for reversal of anticoagulation and reduction in blood loss [9].

Intravenous bolus andexanet administration reversed rivaroxaban-induced anticoagulation as measured by plasma anti-fXa activity (97% decrease), prothrombin time (PT; 77% decrease), and unbound fraction of the anticoagulant (93% decrease); these PD markers correlated with reduction of blood loss (76% decrease) as compared to vehicle controls. Administration of rfVIIa or 3-factor PCC had no effect on blood loss, anti-fXa activity, or plasma free fraction of rivaroxaban. The administration of rfVIIa reduced PT in non-anticoagulated (36% decrease) and in rivaroxaban-anticoagulated (89% decrease) animals, but the reduced PT was not associated with any reduction in bleeding.

To develop a more demanding model, the rabbit liver laceration model was modified such that andexanet was administered after initiation of blood loss in a setting of active bleeding [8]. Andexanet was administered over a wide dose range (5–75 mg/rabbit) in an effort to identify the stoichiometric ratio of andexanet to total rivaroxaban concentration needed to decrease blood loss. In this study, the lowest effective dose of andexanet (35 mg) that showed a significant decrease in blood loss reduced the anti-fXa activity, the plasma free fraction of rivaroxaban, and the increase in PTs by an average of 97%, 99%, and 90%, respectively. Taken together, the results from these two different pre-clinical bleeding models demonstrate a strong correlation between reversal of anti-fXa activity, decrease in free fraction of anticoagulant, and decrease in blood loss. These data support the hypothesis that andexanet rapidly binds and sequesters the FXa inhibitor, thus reversing the anticoagulant effect of FXa inhibition and allowing for the return of thrombin generation, which mediates restoration of normal hemostatic mechanisms. In addition, these data demonstrate that although rfVIIa and PCCs may affect PT or activated Partial Thromboplastin Time (aPTT) measurements, neither of these markers correlate with a decrease in blood loss.

The nonclinical data demonstrate that reversal of anticoagulation by andexanet (as assessed by relevant PD measures) can restore hemostasis and thereby reduce bleeding.

1.3.2. Nonclinical Toxicology and Safety

Good Laboratory Practice (GLP) toxicology studies have been conducted in both the rat and cynomolgus monkey. Andexanet was evaluated in two 14-day repeat dose toxicology studies, one each in rat and monkey. Both toxicology studies administered andexanet twice a day (BID) as a maximal feasible dose (60 mg/kg/day) either daily for 14 days (rats) or every third day (cynomolgus monkeys), followed by a 28-day recovery period. There were no test article-related adverse effects in either study. In the more relevant species, cynomolgus monkeys, the animals were administered andexanet in the presence and absence of a FXa inhibitor (rivaroxaban, apixaban, betrixaban, or enoxaparin). The only significant finding in the 14-day repeat bolus IV study was a male monkey, dosed 60 mg/kg/day with andexanet, who on Day 13 of the study (last dose) experienced anaphylaxis immediately after dosing. This animal recovered with administration of antihistamines and epinephrine. Based on the lack of adverse findings in both species at the highest doses tested, the No Observed Adverse Effect Level (NOAEL) dose in rat and cynomolgus monkeys is 60 mg/kg/day.

As might be expected after repeated dosing with a foreign protein in an animal species, all groups of monkeys and rats receiving andexanet developed antibodies to andexanet that persisted to the end of the 4-week recovery period. Despite the presence of these antibodies, andexanet was still able to reverse the anticoagulant effect of FXa inhibitors from Day 1 to Day 14 in cynomolgus monkey studies *in vitro* or *in vivo*. Antibody development in both rat and cynomolgus monkey studies did not change the toxicokinetics of andexanet from Day 1 to Day 14. Russell's Viper Venom Time (RVVT) was used to measure antibody production against endogenous FX or FXa, and no changes suggestive of antibodies against FX or FXa were observed in RVVT measurements in monkeys administered andexanet.

There were no adverse findings in the male rat central nervous system and respiratory safety pharmacology studies up to, and including, the maximum feasible daily dose of 60 mg/kg when administered by IV bolus. Additionally, andexanet was evaluated for cardiovascular safety as a component study of the 14-day repeat IV bolus study in cynomolgus monkeys and was found not to affect electrocardiographic or blood pressure parameters.

Analysis of the plasma samples from the monkey GLP toxicology study, as well as additional non-GLP monkey studies using a sensitive assay, demonstrated a D-dimer (fibrin degradation product) and Thrombin-Antithrombin (TAT) profile similar to that found in the Phase 1 study (11-501). No assay for prothrombin fragment 1+2 (F1+2) was found to be suitable in cynomolgus monkeys. In addition, it was found that the elevations in TAT and D-dimer associated with andexanet were transient, and these markers returned to baseline more rapidly in monkeys treated with the FXa inhibitor rivaroxaban.

The current hypothesis for the increase in activation of coagulation markers is that andexanet binds to circulating, and possibly vascular-bound, Tissue Factor Pathway Inhibitor (TFPI). The consistency in coagulation markers observed between the GLP toxicology and Phase I clinical study indicate that the monkey is an appropriate species to characterize the safety of andexanet. More importantly, in the GLP toxicology and investigational studies, despite the increases in TAT and D-dimer, there was no histopathological evidence of test article-related thrombus formation. Tissues from the andexanet-treated animals were carefully evaluated for the presence of intravascular thrombi histopathologically in cynomolgus monkeys (n=30 active and n=10 controls), a species in which there were increases in D-dimer and TAT similar to those observed in humans. All tissues were examined by hematoxylin and eosin, and all tissues from the high dose group (60 mg/kg/day treated for 14 days, n=10) and vehicle dose group (n=10) were additionally examined with phosphotungstic acid-hematoxylin for histochemical evidence of intravascular fibrin deposition. The vehicle dose group and the andexanet-treated group were equivalent. An additional GLP toxicology study was conducted in which andexanet was administered to cynomolgus monkeys anticoagulated with apixaban or betrixaban. Results from this study were consistent with earlier findings. Additional details from these studies can be found in the andexanet Investigator's Brochure.

1.4. Summary of Relevant Clinical Experience with Andexanet

Andexanet has been studied in 211 healthy subjects. The trials include a completed single ascending dose Phase 1 study (Study 11-501) in healthy subjects, as well as a number of studies in combination with FXa inhibitors, including a Phase 1 study comparing the PK and PD of andexanet in younger vs. older subjects receiving apixaban (Study 14-506), the Phase 2 dose-range finding Study 12-502 (apixaban, rivaroxaban, edoxaban, and enoxaparin) and the confirmatory Phase 3 studies in healthy older subjects (50–75 years) with apixaban (Study 14-503) and rivaroxaban (Study 14-504), respectively. Summaries of the clinical studies are presented in the Investigator's Brochure.

1.4.1. Phase 1 Study of Andexanet Alone in Healthy Subjects

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 one of four 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 1.4.5.

1.4.2. Phase 1 Study of Andexanet in Healthy Younger versus Older Subjects

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 in older and younger subjects were similar.

1.4.3. Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects

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 one of four 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 are 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. Healthy subjects were then followed through Study Day 13 in a domiciled Phase 1 study unit and, subsequently, through Day 48 as outpatients.

Apixaban (Module 1) was administered at a dose of 5 mg orally (PO) twice each day for 5.5 days, rivaroxaban (Module 2) was administered at a dose of 20 mg PO once daily (QD) for 6 days, enoxaparin (Module 3) was administered at a dose of 40 mg subcutaneously (SQ) QD for 6 days, and edoxaban (Module 4) was administered at dose of 60 mg PO once daily. Andexanet was administered on Day 6, (3 hours after the anticoagulant dose [C_{max}]).

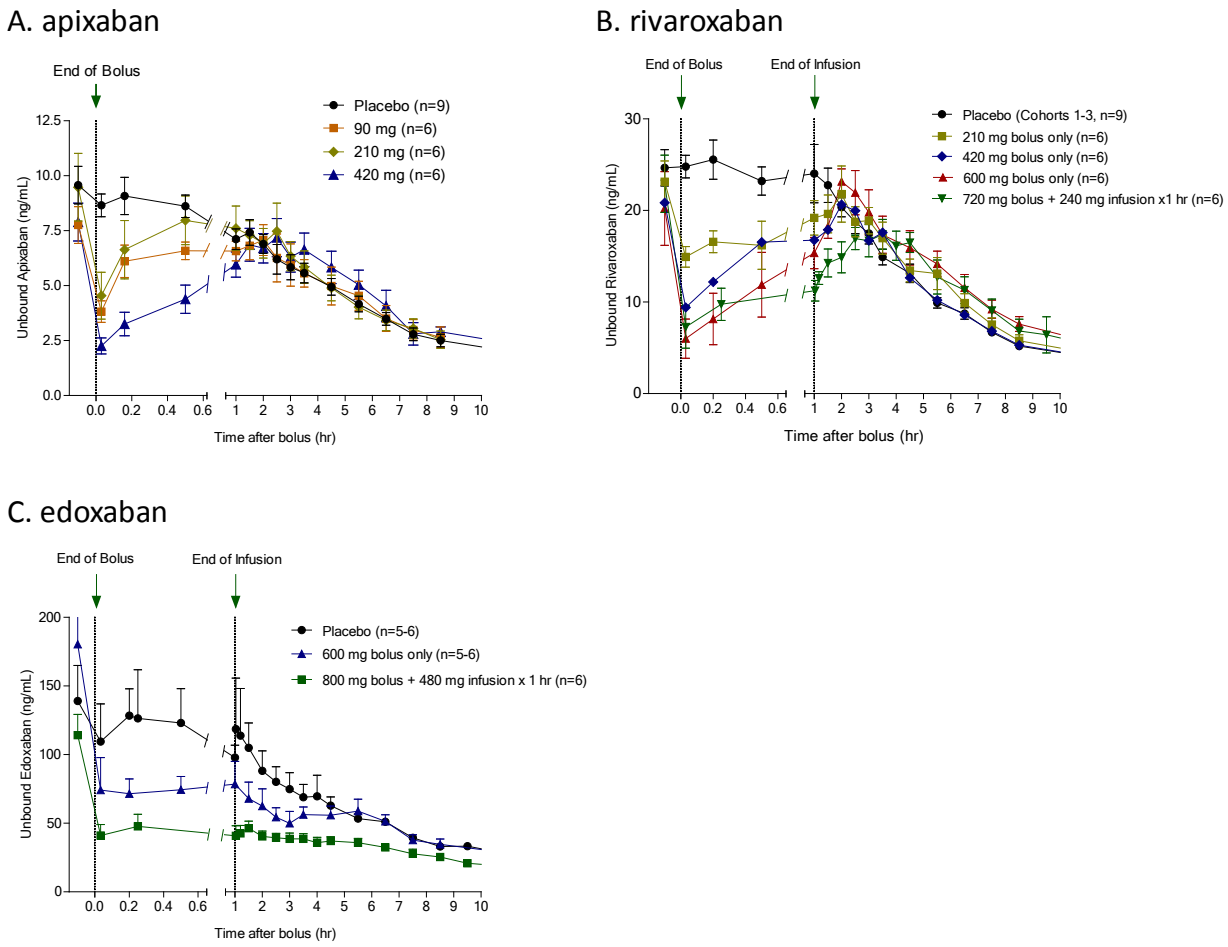
The total dose of andexanet across dosing cohorts ranged from 90 mg to 1,760 mg. These cohorts have evaluated several dosing regimens: single bolus, double bolus, and bolus followed by a continuous infusion. The regimens evaluated in the apixaban module were single boluses of 90 mg, 210 mg, and 420 mg; a double bolus regimen (420 mg bolus + 180 mg bolus), and a 420 mg bolus followed either by a 180 mg infusion (administered over 45 minutes) or by a 480 mg infusion (administered over 120 minutes). The regimens evaluated in the rivaroxaban module were single boluses of 210 mg, 420 mg, and 600 mg; a 720 mg bolus followed by a 240 mg infusion (administered over 60 minutes), and an 800 mg bolus followed by a 960 mg infusion (administered over 120 minutes). The regimens evaluated in the enoxaparin module were single bolus doses of 210 mg and 420 mg. The regimens evaluated in the edoxaban module included bolus doses of 600 mg, and an 800 mg bolus followed by a 480 mg infusion administered over 60 minutes (8 mg/min), and an 800 mg bolus given 5 hours after the last edoxaban dose.

Andexanet exhibited dose-proportional PK for both C_{max} and Area Under the Curve (AUC) with a mean terminal $t_{½}$ of approximately 5 hours and an effective (biological) $t_{½}$ of approximately 50 to 60 minutes.

Administration of andexanet was associated with a rapid decrease in unbound apixaban, rivaroxaban, and edoxaban that was dose-dependent, with the greatest effect observed at the highest doses tested (420 mg dose for apixaban, and 800 mg dose for rivaroxaban and edoxaban) (Figure 2 and Figure 4). The effect of andexanet on plasma unbound apixaban, rivaroxaban, and edoxaban was immediate (i.e., within 2 minutes following completion of andexanet administration) (Figure 2). When andexanet was administered as a bolus followed by a 45-minute continuous infusion (180 mg infusion), or a 120-minute continuous infusion (480 mg

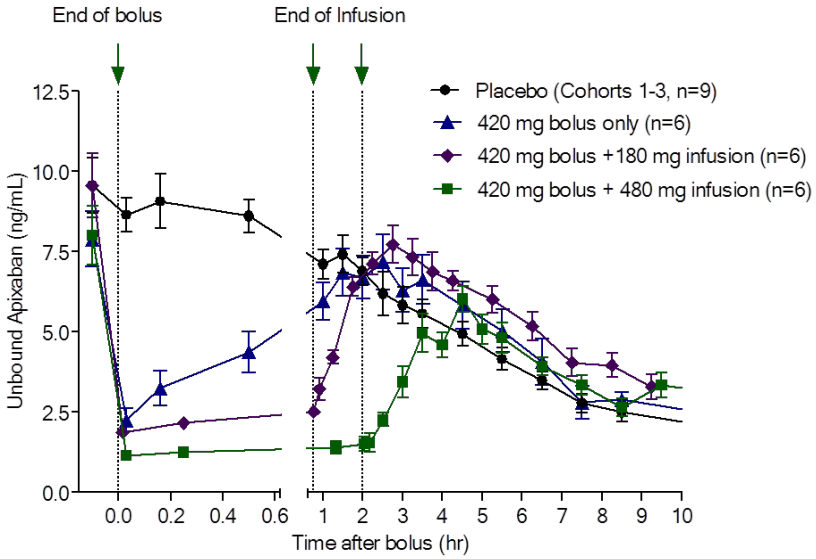
infusion) (Figure 3), the decrease in unbound (free fraction) apixaban was sustained. A continuous infusion of andexanet (960 mg infusion) resulted in a sustained decrease in unbound rivaroxaban (Figure 4). Similarly, a continuous infusion of andexanet (480 mg infusion) resulted in a sustained decrease in unbound edoxaban (Figure 2).

Figure 2: Rapid Onset and Dose-dependent Reduction of Unbound Apixaban, Rivaroxaban, and Edoxaban (12-502)



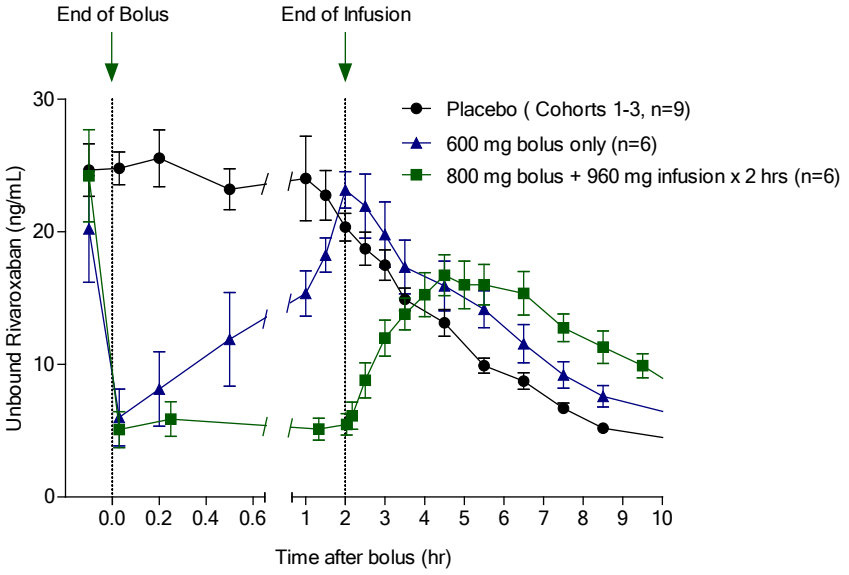
A. Apixaban was administered 5 mg orally (PO) twice a day (BID) for 5.5 days; andexanet was administered on Day 6 with a 90 mg, 210 mg, or 420 mg IV bolus. **B.** Rivaroxaban was administered 20 mg once daily (QD) for 6 days; andexanet was administered on Day 6 with a 210 mg, 420 mg, 600 mg IV bolus, or a 720 mg IV bolus + 240 mg infusion (60 minutes at 4 mg/min). **C**. Edoxaban was administered 60 mg once daily (QD) for 6 days; andexanet was administered on Day 6 with a 600 mg IV bolus, or an 800 mg IV bolus + 480 mg infusion (60 minutes at 8 mg/min). Andexanet administration was timed with the approximate steady-state C_{max} of each anticoagulant (3 hours after the last dose). Data are shown as mean ± standard error of the mean (SEM).

Figure 3: Sustained Reversal of Unbound Apixaban (12-502)



Note: Apixaban was administered 5 mg orally (PO) twice a day (BID) for 5.5 days. Andexanet administration was timed with the approximate C_{max} of apixaban on Day 6 and administered as a 420 mg IV bolus, 420 mg bolus + 180 mg infusion (45 minutes at 4 mg/min), or 420 mg bolus + 480 mg infusion (120 minutes at 4 mg/min). Data are shown as mean ± Standard Error of the Mean (SEM).

Figure 4: Sustained Reversal of Unbound Rivaroxaban (12-502)

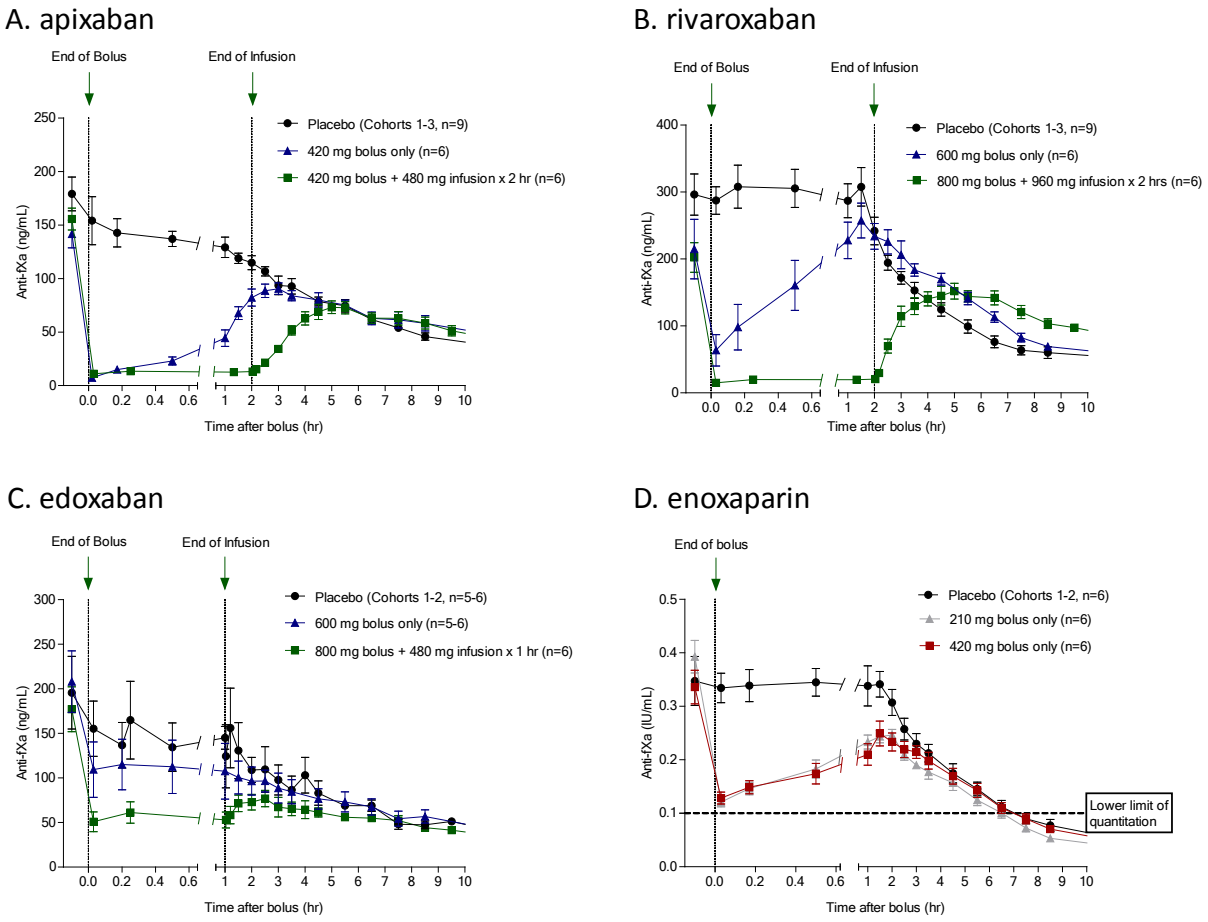


Note: Rivaroxaban was administered 20 mg once daily (QD) for 6 days; andexanet was administered on Day 6 with a 600 mg or an 800 mg IV bolus + 960 mg infusion (120 minutes at 8 mg/min). Andexanet administration was timed with the approximate steady-state C_{max} of the anticoagulant (3 hours after the last dose). Data are shown as mean ± Standard Error of the Mean (SEM).

For apixaban, rivaroxaban, edoxaban, and enoxaparin, administration of andexanet resulted in a dose-dependent reduction in anti-fXa activity (Figure 5). "Baseline" was defined as the time immediately prior to andexanet administration, which occurred 3 hours following the last anticoagulant dose (the anticoagulant steady-state C_{max}).

Additionally, apixaban, rivaroxaban, edoxaban, and enoxaparin inhibited thrombin generation relative to the pre-anticoagulant baseline (Study Day 1) (Figure 6). These anticoagulant effects of apixaban, rivaroxaban, and edoxaban were reversed in a dose-dependent fashion by administration of andexanet. These effects are consistent with restoration of hemostatic mechanisms after andexanet administration. The safety data from this study are summarized in Section 1.4.4.

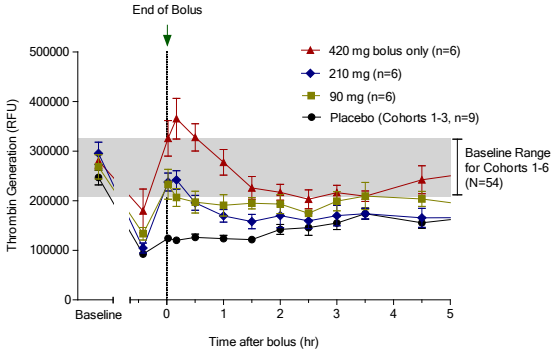
Figure 5: Rapid Onset and Reduction of Anti-fXa Activity (12-502)

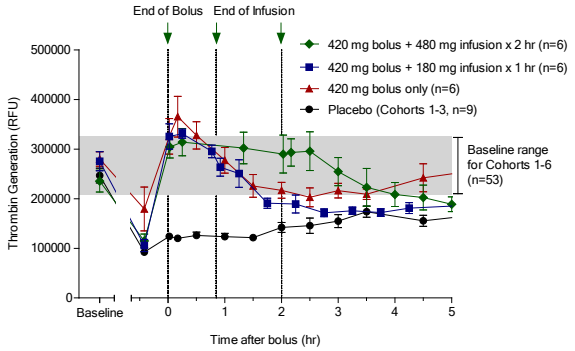


A. Apixaban was administered at 5 mg orally (PO) twice a day (BID) for 5.5 days; andexanet was administered on Day 6 as a 420 mg IV bolus or 420 mg IV bolus + 480 mg infusion (120 minutes at 4 mg/min). **B.** Rivaroxaban was administered at 20 mg once daily (QD) for 6 days; andexanet was administered on Day 6 as either a 600 mg IV bolus or an 800 mg IV bolus + 960 mg infusion (120 minutes at 8 mg/min). **C.** Edoxaban was administered at 60 mg once daily (QD) for 6 days; andexanet was administered on Day 6 as either a 600 mg IV bolus or an 800 mg IV bolus + 480 mg infusion (60 minutes at 8 mg/min). **D.** Enoxaparin was administered at 40 mg subcutaneously (SQ) QD for 6 days; andexanet was administered on Day 6 as a 210 mg or 420 mg IV bolus. Andexanet administration was timed with the approximate steady-state C_{max} of each anticoagulant (3 hours after the last dose). Data are shown as mean ± standard error of the mean (SEM).

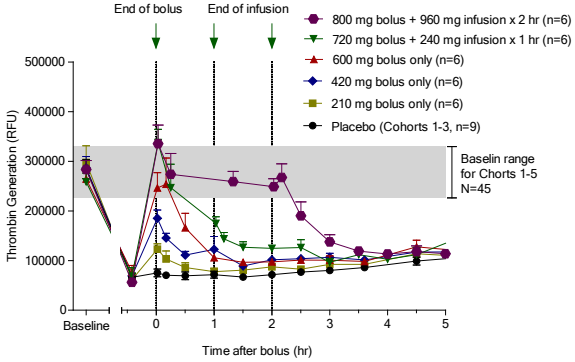
Figure 6: Reversal of FXa Inhibitor-induced Inhibition of Thrombin Generation (12-502)

A. apixaban

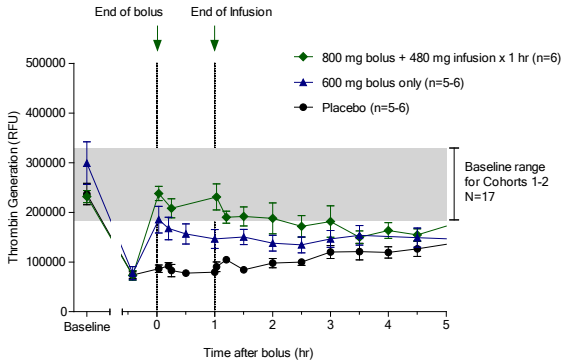




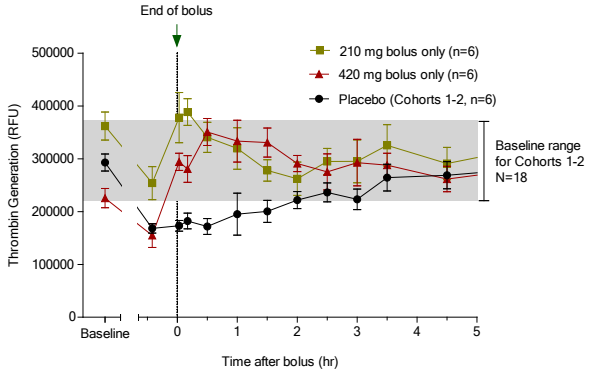
B. rivaroxaban



C. edoxaban



D. enoxaparin

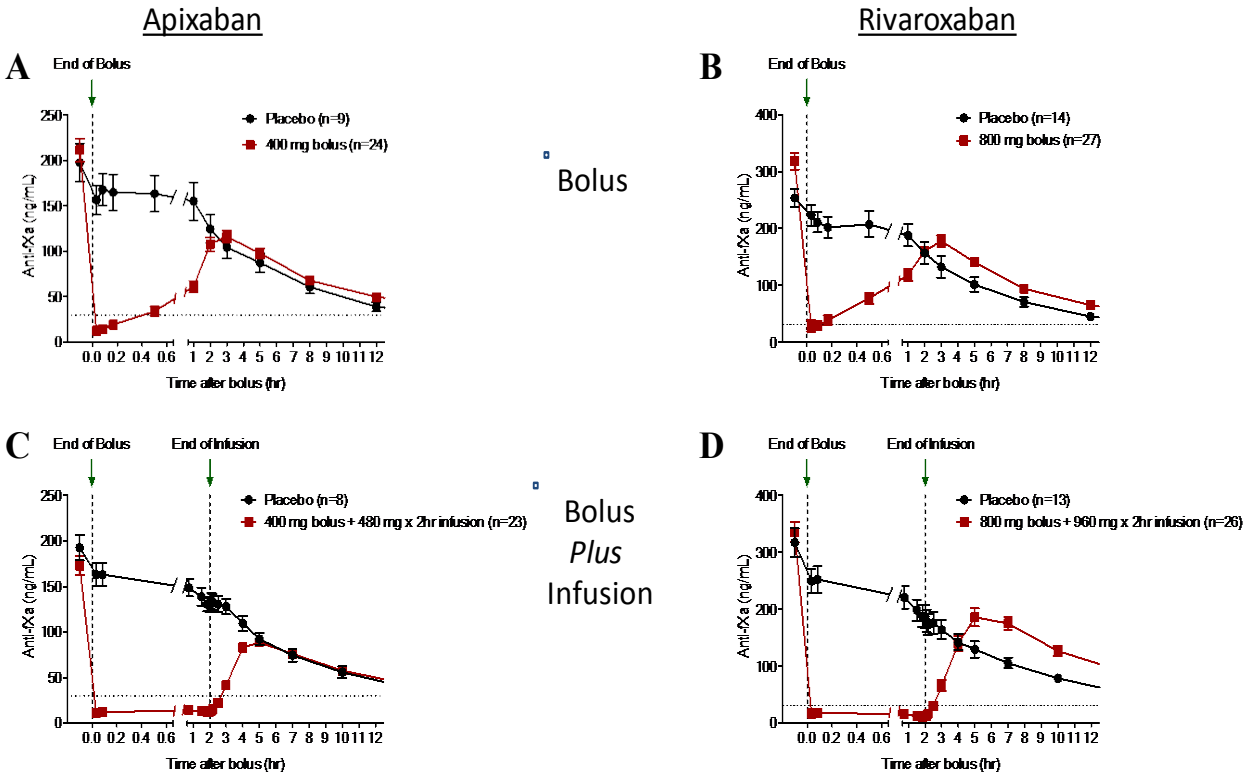


A. With apixaban, andexanet was administered as a 90 mg, 210 mg, 420 mg IV bolus; a 420 mg bolus + 180 mg continuous infusion (45 minutes at 4 mg/min); or a 420 mg bolus + 480 mg continuous infusion (120 minutes at 4 mg/min). **B.** With rivaroxaban, andexanet was administered as a 210 mg, 420 mg, 600 mg IV bolus; a 720 mg IV bolus + 240 mg continuous infusion (60 minutes at 4 mg/min); or a 800 mg IV bolus + 960 mg continuous infusion (120 minutes at 8 mg/min). **C.** With edoxaban, andexanet was administered as a 600 mg IV bolus; or an 800 mg IV bolus + 480 mg continuous infusion (60 minutes at 8 mg/min). **D.** With enoxaparin, andexanet was administered as a 210 mg or 420 mg IV bolus. Data are shown as mean ± standard error of the mean (SEM). Baseline range was based on thrombin generation (mean ± standard deviation [SD]) on Day 1 prior to dosing of anticoagulant.

1.4.4. Phase 3 Studies in Healthy Older Volunteers

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) [30]. 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 while domiciled in a Phase 1 study unit and, subsequently, through Day 43 as outpatients. In both studies, andexanet was administered either as an IV bolus (Part 1) or an IV bolus plus a continuous infusion for 120 minutes (Part 2). Reversal of anticoagulation was measured using anti-fXa activity, anticoagulant free fraction, thrombin generation, and other coagulation markers. A single IV bolus of andexanet rapidly and significantly reversed the anti-fXa activity of apixaban and rivaroxaban (Figure 7), reduced unbound apixaban and rivaroxaban concentrations (Figure 8), and restored normal thrombin generation (Figure 9). These effects were sustained by the follow-on infusion.

Figure 7: Rapid Onset and Significant Reduction of Apixaban and Rivaroxaban Anti-fXa Activity in Older Healthy Subjects by Andexanet

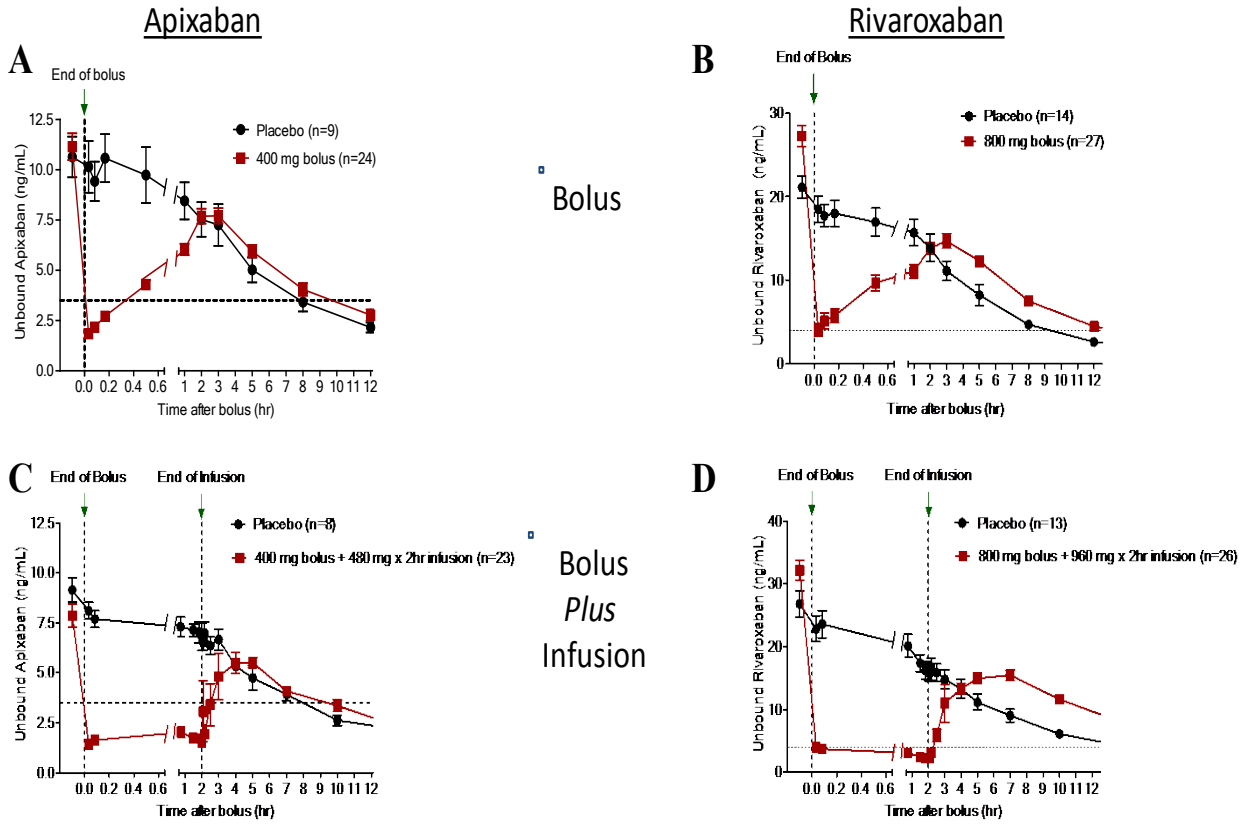


Legend: Anti-fXa activity was measured prior to and after andexanet or placebo administration on study Day 4. Dashed lines indicate the end of bolus or infusion.

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 [12].

Figure 8: Rapid Onset and Significant Reduction of Free Apixaban and Rivaroxaban Concentrations in Older Healthy Subjects by Andexanet

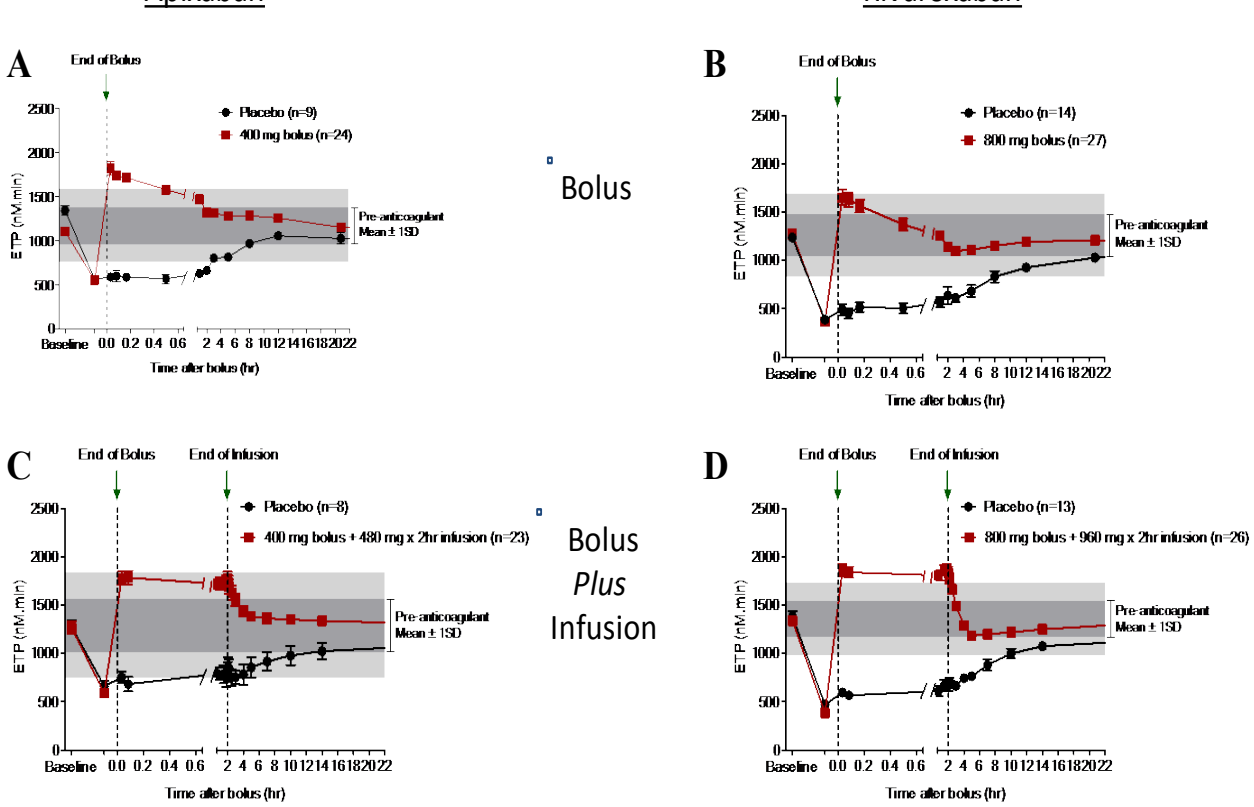


Legend: A break in the X axis was added to better visualize the immediate, short-term dynamics of unbound inhibitor plasma concentration following andexanet treatment. The horizontal line represents the calculated no-effect level for anticoagulant activity (3.5 ng/mL of apixaban and 4 ng/mL of rivaroxaban). The points on the graph represent the mean unbound inhibitor plasma concentrations and error bars illustrate standard error. There was a statistically significant difference ($P < 0.05$) between andexanet and placebo until 2 hours or 3 hours after the end of the bolus, and until 1 hour or 3 hours after the end of the infusion in apixaban- or rivaroxaban-treated subjects, respectively.

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: Plasma concentrations of unbound apixaban or rivaroxaban were measured prior to and after andexanet or placebo administration on study Day 4.

Figure 9: Restoration of Thrombin Generation by Andexanet in Older Healthy Subjects Anticoagulated with Apixaban or Rivaroxaban



ETP = Endogenous thrombin potential. Thrombin generation was assessed before and after administration of andexanet or placebo by measurement of ETP.

Legend: A break in the X axis was added to better visualize the immediate, short-term dynamics of ETP following andexanet treatment. The dark shaded area represents 1 standard deviation above and below the baseline mean. The light shaded area represents 2 standard deviations above and below the baseline mean. Baseline refers to ETP on Day 1 prior to any anticoagulant administration. A value greater than the baseline mean minus 1 standard deviation was pre-specified to indicate restoration of thrombin generation and the other limits were included post hoc. The points on the graph represent the mean ETP value and error bars illustrate standard error. There was a statistically significant difference ($P < 0.001$) between andexanet and placebo for at least 12 hours after administration of bolus (Part 1) or infusion (Part 2).

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.

The results from the Phase 3 studies of apixaban and rivaroxaban were very similar to results obtained in the Phase 2 study, demonstrating the reproducibility of andexanet's ability to reverse inhibition of FXa activity. This reproducibility of the data allowed Portola to use PK-PD modeling to select doses of andexanet for reversal of edoxaban and enoxaparin.

1.4.5. Summary of Safety from Clinical Studies

Andexanet has been generally well tolerated in healthy volunteers in the Phase 1, 2, and 3 studies at the doses studied (i.e., total doses of 30 mg, 90 mg, 210 mg, 300 mg, 420 mg, 600 mg, 900 mg, 960 mg, and 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. This SAE, which was deemed by the Investigator as unlikely to be related to andexanet, occurred 18 days after andexanet dosing in a subject treated at a dose of 30 mg. No severe or life-threatening AEs have been reported. No Thrombotic Events (TEs) have been reported in any of the healthy volunteer studies. Infusion reactions have been mild to moderate in severity, do not appear to be dose dependent and have rarely required treatment (2 healthy subjects received one dose each of diphenhydramine). With the exception of two healthy 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 F1+2, TAT, and D-dimer and with concomitant decrease in TFPI levels, all of which reversed after discontinuation of andexanet. These changes returned to baseline on average by 4 days after discontinuation of andexanet. These findings were not associated with a clinical TE in any subject. 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 apixaban, rivaroxaban, enoxaparin, and edoxaban.

Among healthy subjects treated with andexanet, 12.1% developed low-titer non-neutralizing antibodies to andexanet. However, there have been no neutralizing antibodies, nor antibodies to native FX or FXa.

2.0 STUDY OBJECTIVES

In FXa-inhibitor treated patients with acute major bleeding and reduced factor Xa activity, the objectives of this study are as follows:

2.1. Primary Efficacy Objectives

In FXa-inhibitor treated patients with acute major bleeding with reduced FXa activity, the objectives of this study are as follows:

- To demonstrate the decrease in anti-fXa activity following andexanet treatment.
- To evaluate the hemostatic efficacy following andexanet treatment.

2.2. Secondary Efficacy Objective

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

2.3. Exploratory Efficacy Objectives

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

2.4. Safety Objectives

- To evaluate the overall safety of andexanet including: adverse events, adjudicated Thrombotic Events (TEs) and deaths, vitals, clinical laboratory measurements, and antibodies to FX, FXa, and andexanet.
- To evaluate the 30-day all-cause mortality.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a multicenter, prospective, open-label study of andexanet in patients presenting with acute major bleeding who have recently received one of the following FXa inhibitors: apixaban, rivaroxaban, edoxaban, or enoxaparin. Attempts will be made to enroll patients on direct FXa inhibitors as well as those on indirect FXa inhibitors, and to limit the percentage of enrolled patients receiving indirect FXa inhibitors to ≤ 20%. A minimum of approximately 110 evaluable patients with ICH, 50 of whom are considered to be high-risk as determined by the core lab, will be enrolled in the study. In order to achieve sufficient numbers of ICH patients, enrollment in other subgroups (e.g., patients with non-ICH bleeds) may be capped by the Sponsor.

Once consent is obtained and eligibility criteria are confirmed, patients with acute major bleeding will receive andexanet as an IV bolus administered over ~15 to 30 minutes, followed immediately by a continuous infusion administered over ~120 minutes. The start of the andexanet bolus must be within 18 hours following the last dose of FXa inhibitor, if the timing of the last dose is known, designed to ensure patients have therapeutic anti-fXa activity levels. If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible—following the signing of the ICF and completion of pre-treatment procedures—but no later than 3 hours following the signing of the ICF**.**

Patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received (see Section 6.2) and the dose and timing of the most recent dose. For anti-fXa activity and diagnostic evaluations to support hemostatic efficacy (e.g., imaging tests, hemoglobin levels), baseline is defined as the most recent assessment prior to the start of the andexanet bolus. For post-baseline assessments, time 0 is defined as the end of the continuous andexanet infusion. Adverse Events and survival will be followed through the Day 30 post-treatment visit.

An independent Endpoint Adjudication Committee (EAC), governed by processes and criteria defined in an Adjudication Charter, will adjudicate bleeding entry criteria, hemostatic efficacy, re-bleeding events, deaths, potential TEs, and AEs of special interest. Hemostatic efficacy will be evaluated using the rating system from Sarode, et al. [5], described in Appendix B. The EAC will be blinded to all anti-fXa levels. In addition, re-bleeding episodes will be adjudicated according to the following definition: recurrent bleeding either from the same or a different anatomical site, in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. Ratings of excellent, good, poor/none, or non-evaluable (either administrative or non-administrative) will be assigned for various sites of bleeding and will be based upon pre-defined rating criteria. Bleed type categories include: ICH (e.g., intracerebral [intraparenchymal and intraventricular], subarachnoid, and subdural), pericardial, intra-spinal, and other non-visible bleeding (such as gastrointestinal, genitourinary, retroperitoneal, and intrathoracic bleeding). The criteria for determination of efficacy are detailed in Appendix B and are based upon the collection of objective assessments at baseline

and specified time points through the 12 hours post administration of andexanet. Assessments include but are not limited to the following: CT or MRI and clinical metrics (Glasgow Coma Scale, modified Rankin Score, National Institutes of Health Stroke Scale) at baseline, 1 hour and 12 hours for ICH, MRI/CT for spinal bleeds (within 12 hours); echocardiogram for pericardial bleed (within 12 hours); and transfusion-corrected hemoglobin and hematocrit for other non-visible bleeding (baseline through 12 hours). Other procedures performed on subjects relevant to the subject status may be collected for the purpose of adjudication. Site non-compliance due to missing assessments (i.e., assigned rating of non-evaluable due to missing assessment for reasons other than death) is considered a notable significant deviation on the part of the investigator/site.

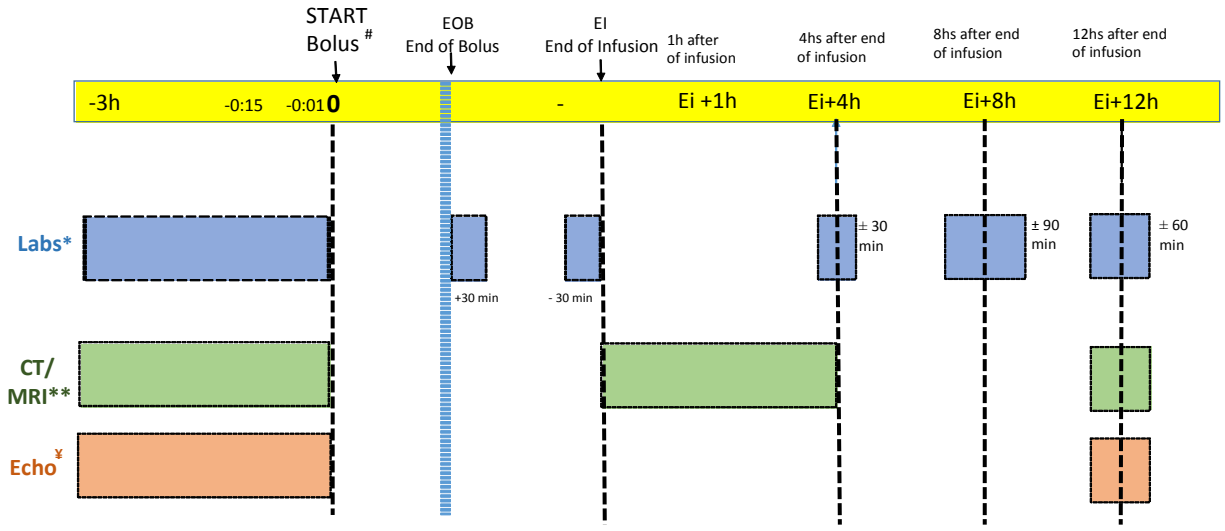
Reversal of anticoagulation will be evaluated by measuring anti-fXa activity (first primary objective) and unbound anticoagulant plasma levels (for apixaban, edoxaban, and rivaroxaban). Additional tests, such as thrombin generation (both with TF-initiated and non-TF-initiated forms of the assay), TFPI, and ATIII antigen levels will be used to help assess the state of coagulation.

The protocol provides guidance for Packed Red Blood Cell (PRBC) transfusion, transfusion of other blood products, and administration of coagulation factors (see Section 7.0).

An independent Data Safety Monitoring Board (DSMB) will review all safety data on a schedule described in the DSMB Charter.

A detailed schedule of events can be found in Appendix A and a schematic of the first 12 hours of Day 1 can be found in Figure 10.

Figure 10: Study Schematic



* A detailed listing of study procedures including additional lab sample post Ei+12 hours through Day 30 is detailed in Appendix A.

** CT/MRI are required for ICH and intra-spinal patients. The Ei+1 hour scan (window Ei + 4 hours) is required for ICH only.

¥ Pericardial bleeds only.

Re-dosing procedures begin prior to the start of the 2nd bolus for measurement of anti-fXa activity.

3.2. Blinding and Randomization

3.2.1. Randomization

This study is not randomized.

3.2.2. Blinding

The study is open-label. All patients will receive andexanet, although the dose is different based on the FXa inhibitor the patient has received and the dose and timing of the most recent dose.

3.3. Duration of Study

The study duration for any individual patient will be up to 37 days. There are 4 study periods as follows (includes circumstances where re-dosing may have been deemed necessary):

- Screening Period: < 1 day (Day 1).
- Treatment Period: < 1 day (Day 1).
  - 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 Evaluation Period including Follow-up Period (AEs, survival): 30 days (Day 1 to the Day 30 study visit).

3.4. Discussion of Study Design

3.4.1. General Comments

There is no available standard of care for reversal of anticoagulation from FXa inhibitor drugs. Due to this, randomized active comparator trial designs were not possible. Additionally, in this critically ill population, use of a placebo control was not considered ethical due to the inherent risk of serious morbidity and mortality from uncontrolled acute major bleeding. Furthermore, because this study is expected to be ongoing after regulatory approval of andexanet under an accelerated approval pathway, any study with a control arm perceived as inferior would be difficult to enroll because commercial drug would be available as an option. Based on these considerations, a single arm study design was selected.

3.4.2. Study Population

The study will enroll patients who have recently taken a FXa inhibitor (i.e., within 18 hours or at an unknown time) and who present with an acute major bleeding episode.

In order to enroll a population that will be similar to the intended target population for andexanet, the eligibility criteria have few restrictions on comorbid conditions. For example, there is no upper age limit or lower limit for renal function. There are also no restrictions on concomitant medications, other than the use of warfarin or dabigatran, which are restricted because andexanet does not reverse anticoagulation from these drugs. Patients on prophylactic dose enoxaparin are excluded because the likelihood that bleeding related to enoxaparin in this population is low. For patients on a known enoxaparin dose, the minimum dose allowed is the renal impairment treatment dose for VTE – this allows the higher risk patients with renal impairment to participate. Patients with known selected hypercoagulable states and recent TEs (i.e., within 2 weeks) are excluded because of their increased risk for TEs, especially if anticoagulation is reversed. Finally, patients who have received procoagulant products (e.g., PCC, rFVIIa) within 7 days are also excluded because of their higher risk of TE.

Due to their anatomic location and spatial constraints, ICH bleeds have a markedly poor prognosis, even in relationship to other major bleeding events [13]. Patients with ICH therefore have the greatest unmet medical need. Accordingly, to more comprehensively evaluate the efficacy and safety of andexanet in this particularly vulnerable subset of bleeds, the study population will be enriched for ICH patients. A minimum of approximately 110 evaluable ICH patients, 50 of whom are deemed by the core lab to be high risk (based on criteria defined in Section 11.8) will be enrolled in the study. In order to achieve sufficient numbers of ICH patients, enrollment in other subgroups (e.g., patients with non-ICH bleeds) may be capped.

In addition, because there is no standardized clinical assay for anti-fXa activity, it is not possible to use anti-fXa activity as a marker of anticoagulation for purposes of enrollment into the study. However, samples for anti-fXa activity (as well as for anticoagulant plasma free fraction and thrombin generation) are being collected for later analysis at a central laboratory. As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of FXa inhibitor within 18 hours if the timing is known. (If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible–following signing of the ICF and completion of pre-treatment procedures–but no later than 3 hours following signing of the ICF.) The 18-hour time point was selected to enroll the maximum number of patients while avoiding enrolling a large number of patients who are non-evaluable for the primary efficacy analysis due to low anti-fXa activity levels. The 18-hour time point is the approximate time, following a dose of rivaroxaban, to a plasma concentration that is approximately equal to twice the mean trough level at 24 hours. From Study 12-502, it was empirically determined that, at these concentrations, anti-fXa activity is still elevated and thrombin generation is still suppressed. Therefore, it is likely that there is an increased risk of bleeding within this 18-hour window, which is likely the result of FXa inhibition or aggravated by FXa inhibition.

Only patients who are determined to have effective levels of anticoagulation will be considered evaluable for efficacy purposes. For apixaban and rivaroxaban, an anti-fXa activity level of ≥ 75 ng/mL (as determined by central laboratory evaluation) was selected. This level corresponds to anti-fXa activity achieved at twice the mean plasma rivaroxaban concentration at 24 hours after administration of the highest approved doses of anticoagulant (mean 44 ng/mL, 5th and 95th percentile range, 12-137 ng/mL) [14]. Similarly, for apixaban, 75 ng/mL represents the anti-fXa level achieved at twice the mean plasma apixaban concentration at 12 hours following a 5 mg dose based on data from the 12-502 study. These converging data form the basis of the selected anticoagulant last dose window and cutoff for anti-fXa level.

For edoxaban, a cutoff of 75 ng/mL had been used in earlier protocol amendments. However, preliminary data from the ongoing study has revealed that 80% of edoxaban-treated patients had an anti-fXa activity below this threshold. Furthermore, an anti-fXa activity of 40 ng/mL was the approximate level in the pivotal ENGAGE-AF study at which the risk of life-threatening or fatal bleeding exceeds the risk of an ischemic stroke [Edoxaban Ad Comm September 2014]. Therefore, given the above considerations, an anti-fXa activity level of ≥ 40 ng/mL will be used to determine efficacy evaluability.

The enoxaparin anti-fXa cutoff level of 0.50 IU/mL implemented in earlier versions of the protocol was based on an estimated steady state trough level [15] following 1 mg/kg treatments. However, data from the ongoing study noted that 28% of enoxaparin treated patients had anti-fXa below 0.50 IU/mL. In order to avoid excluding large numbers of enoxaparin-treated patients from the efficacy analysis, the anti-fXa cutoff has been revised to 0.25 IU/mL. This is

consistent with the expected anti-fXa level for the enoxaparin elimination half-life (~7 hours) and the above mentioned 18 hour inclusion criteria. In addition, anti-fXa levels at > 0.20 IU/mL are related to increased bleeding risk in patients treated with 40 mg enoxaparin [1].

Based on these data, efficacy evaluable patients must have a central laboratory-determined anti-fXa activity ≥ 75 ng/mL for patients receiving apixaban and rivaroxaban, ≥ 40 ng/mL for patients receiving edoxaban, and ≥ 0.25 IU/mL for patients receiving enoxaparin.

The definition of major bleeding in the study is based on the ISTH definition [16]. Slight modifications have been made to the definition of major bleeding in order to provide further detail on circumstances for which the use of a reversal agent would be deemed medically necessary. Importantly, to ensure that only patients with a severe and acute presentation are enrolled, only patients who urgently require reversal of anticoagulation are eligible. Patients who are candidates for "watchful waiting" with respect to anticoagulation reversal would not be eligible based on the entry criteria. To ensure uniformity of application of the bleeding entry criteria, the EAC will review source documents to determine eligibility on this criterion. This eligibility review will occur before reviewers are given access to post-baseline data. Patient eligibility, based on the central review, will determine whether or not patients are efficacy evaluable; however, because central reviews cannot occur in real time, the central review decisions will not affect enrollment of patients.

3.4.3. Rationale for the Key Efficacy Endpoints

The Phase 2 and Phase 3 trials of andexanet used reversal of anticoagulation endpoints as assessed by anti-fXa levels, anticoagulant free fraction, and thrombin generation. In this study, both reversal of anticoagulation and a clinical bleeding endpoint are being studied as primary efficacy outcomes.

Anti-fXa Activity

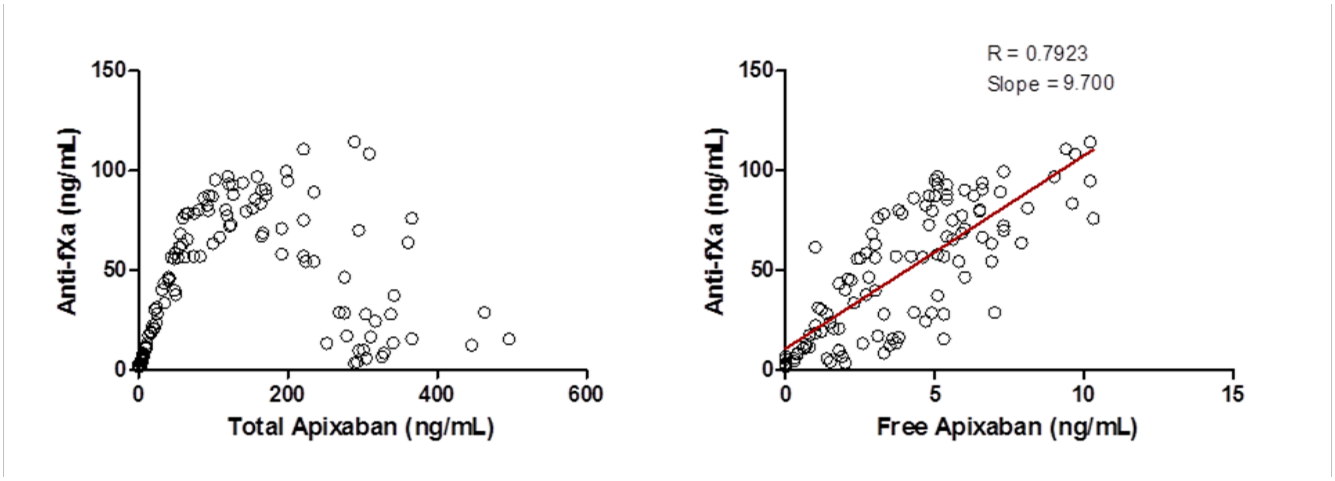
Anti-fXa activity was chosen as the most relevant PD marker for demonstration of reversal of anticoagulation based on several considerations:

- In Phase 2 dose ranging trials with rivaroxaban and apixaban in patients who had undergone total knee replacement surgery or had symptomatic acute venous thrombosis, increasing the dose of the anticoagulant correlated with increased plasma drug concentration and increased frequency and severity of bleeding [17, 18].
- Plasma concentration of a FXa inhibitor correlates well with *ex vivo* anti-fXa activity [19, 20].
- In patients treated with an indirect FXa inhibitor (enoxaparin), severity of bleeding or major bruising can be described as a function of cumulative AUC of anti-fXa activity [21].

- The unbound plasma concentration of apixaban but not total plasma concentration correlates with anti-fXa activity (Figure 11) in subjects treated with andexanet in Study 12-502.
- Only the free, unbound plasma fraction of FXa inhibitor appears to account for the anticoagulant effects of the FXa inhibitors based on a critical level below which anti-fXa activity is lost [22-24].
- In animal models of blood loss, decrease in plasma free fraction of FXa inhibitor and/or anti-fXa activity correlates with reduction in blood loss [17, 25].

As a correlation with the anti-fXa activity, the free/unbound fraction of the direct inhibitors is also monitored at the same time points as anti-fXa activity. Of note, because of the various molecular weights for enoxaparin, there is no assay for measuring unbound enoxaparin levels.

Figure 11: Relationship of Anti-fXa Activity to Total or Free Apixaban Concentration



At this time, it is unknown what degree of reversal of anti-fXa activity is required to impact bleeding in patients receiving FXa inhibitors. However, analysis of the anti-fXa activity and thrombin generation data from all subjects dosed with apixaban (5 mg BID) for 5.5 days showed that normalization of hemostasis (as measured by a thrombin generation assay) was achieved when circulating anti-fXa activity was < 37 ng/mL. This corresponds to an approximate 75% reduction of peak (just prior to andexanet administration) anti-fXa activity. In these subjects anticoagulated with apixaban, average anti-fXa activity from 4 separate cohorts (n=6/cohort) at 2 minutes after the 420 mg IV bolus of andexanet ranged from 6.3 ng/ml to 11.9 ng/ml. This represents an average 94% reduction of peak (just prior to andexanet administration) anti-fXa activity. Similarly large reductions in peak anti-fXa activity levels were achieved for rivaroxaban, edoxaban, and enoxaparin at the planned doses for this study (or lower doses) (Figure 5).

Hemostatic Efficacy—Acute Major Bleeding

There are no validated clinical bleeding endpoints. Because of the heterogeneity of bleeding (e.g., different anatomic locations, different mechanism and severity of injury), it is not possible to use a single modality of measurement to evaluate all bleeding types. The efficacy variable of "effective hemostasis" (Appendix B) chosen for this study is an endpoint originally developed in collaboration with the Food and Drug Administration to support the approval of PCCs (Kcentra) for the treatment of acute major bleeding [5]. The scoring system for effective hemostasis allows for different types of assessments for different bleeding types (e.g., head CT or MRI for ICH, corrected hemoglobin and hematocrit for non-visible bleeding). Because the criteria for the determination of hemostatic efficacy are largely based on objective measures (e.g., CT/MRI, hemoglobin corrected for transfusion), the potential for bias is reduced.

Specifically for ICH, the primary efficacy outcome is based on reducing/preventing the increase in volume and/or thickness of the hemorrhage, as judged by CT/MRI. An excellent hemostatic outcome requires an effect by the 1-hour post-infusion time point that is maintained through the 12-hour time point. Importantly, the time period between the baseline CT/MRI and start of andexanet dosing should be minimized. Otherwise, significant hemorrhage expansion occurring early after baseline imaging counts against hemostatic efficacy even if prior to andexanet administration.

There are currently no clinical endpoints established or validated to evaluate hemostatic efficacy for ICH. Such a clinical endpoint would be extremely difficult to standardize across the different intracranial compartments of bleeding (e.g., intracerebral [intraparenchymal and intraventricular], subarachnoid, subdural) since the clinical presentations and severity of deficits would vary greatly amongst these compartments. Intraventricular hemorrhage expansion generally impacts level of consciousness but may have little impact on focal stroke deficits (NIHSS) (Appendix H) given their midline location. Subdural and subarachnoid hemorrhage expansion would have to be quite large to produce sufficient mass effect to result in focal neurologic symptoms. Amongst intracerebral parenchymal hemorrhages, there is great variability in brain eloquence (specific brain regions that directly control function) which dramatically varies the clinical effects of hemorrhage expansion (i.e., brainstem being much more eloquent than cortex). CT/MRI-based volumetric measurement is thus the most direct way to evaluate hemostatic efficacy. A clinical endpoint for ICH such as neurologic deterioration (defined as National Institutes of Health Stroke Scale [NIHSS] (Appendix H) worsening of 4 or more points or Glasgow Coma Scale [GCS] worsening of 2 or more points) is a more indirect measure of hemostatic efficacy since it is impacted by several factors not related to hemostasis, such as initial hematoma volume, edema, infection, and other medical complications [26]. That said, the best clinical measure of focal neurologic change is captured by the NIHSS (Appendix H) and the best clinical measure of change in consciousness would be captured by the GCS. Modified Rankin scores (mRS) are used to evaluate disability at 3 months and are designed to capture longer term changes in status. The NIHSS (Appendix H), GCS, and mRS

assessments will thus be performed pre-dose and aligned with imaging assessment (1 hour and 12 hours post-dose), as well as the long-term safety follow up (Day 30) for an exploratory assessment of clinical outcome.

Other bleed types that at least partially rely on imaging assessments for hemostatic outcome include pericardial (echocardiogram), retroperitoneal (CT/ultrasound), and intra-spinal (CT/MRI) bleeds.

Hemostatic outcome for GI bleeding is based on hemoglobin, although other data elements are collected including the presence of hematemesis, red blood per rectum, and melena per rectum.

Thrombin Generation and TFPI

In clinical studies in healthy volunteers, TF-initiated thrombin generation was used as a biomarker of restoration of hemostasis. Thrombin is the last protease in the coagulation pathway leading to fibrin formation. Therefore, thrombin generation is a physiologically relevant measurement of both anticoagulation and restoration of hemostasis distal to FXa inhibition. In the Phase 2 study (12-502), reversal of inhibition of thrombin generation by the FXa inhibitors was dose- and regimen-dependent and correlated with reversal of anti-fXa activity. Since andexanet binds to TFPI (see below) and the TF-initiated form of the assay may be affected by this interaction, a non-TF-initiated TG assay will be implemented in Amendment 4 to ascertain the TFPI-independent impact of andexanet on thrombin generation.

TFPI is an endogenous anticoagulant present at low nanomolar plasma concentration that binds to FXa and regulates the activity of the TF-fVIIa complex in the extrinsic coagulation pathway. Similar to FXa-TFPI interaction, andexanet binds to TFPI with high affinity and may exert some effect on the TF-initiated thrombin generation and reversal of anticoagulation.

However, both the clinical and nonclinical data suggest that during the approximately 4 hours of andexanet treatment (bolus, infusion, and immediate [~2 hours] post-infusion period), the predominant mechanisms of action of andexanet are: 1) sequestration of the FXa anticoagulant; 2) decrease in the free fraction of the inhibitor; and 3) reversal of the anti-fXa activity allowing a definitive hemostatic plug to form and stabilize during the first hour after dosing. TFPI inhibition by andexanet during this period is ***not*** the predominant mechanism of anticoagulant reversal and hemostasis, although it may contribute slightly during this initial period by enhancing TF-initiated thrombin generation.

While andexanet is largely cleared after about 5 hours, inhibition of TFPI activity by andexanet may contribute to the *maintenance* of the hemostatic effect for the subsequent 10 to 20 hours. This may be manifested, at least in part, by the sustained normalization of thrombin generation through 24 hours seen in the Phase 3 (and Phase 2) studies – a hypothesis to be investigated in the ongoing studies. For this reason, TFPI antigen levels are implemented in Amendment 4.

TFPI levels and thrombin generation will be evaluated as exploratory efficacy endpoints at various time points through 72 hours post-andexanet dosing.

3.4.4. Rationale for the Dose Regimen

Patients will receive one of two 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 followed by a continuous infusion at 4 mg/min.
- High dose: 800 mg IV bolus followed by a continuous infusion at 8 mg/min.

The continuous infusion will last approximately 120 minutes for all patients. A dosing schema, categorized by FXa inhibitor and time from last dose, is provided in Table 3.

The doses for this Phase 3b/4 study were chosen based on preclinical animal model data and data from actual and modeled data from Study 12-502.

Preclinical models of bleeding, in both the mouse tail transection and rat liver laceration model, demonstrated that a single bolus was capable of controlling bleeding to the levels seen in non-anticoagulated animals.

The doses in this study are within the range of doses and infusion durations studied previously in Study 12-502 and the Phase 3 studies (14-503 and 14-504). Data from the Phase 3 studies with apixaban and rivaroxaban confirm the levels of FXa inhibition and recovery of thrombin generation 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 thrombin generation assay. The change to the lower dose (400 mg) at 8 hours was based on the PK-PD model that predicted the time at which equivalent anti-fXa activity reversal and thrombin generation normalization would be achieved.

In the andexanet Phase 2 study where andexanet was administered to healthy human subjects who had been treated with apixaban 5 mg PO BID, multiple cohorts of both andexanet bolus alone (90 mg, 210 mg, and 420 mg) and bolus + infusion regimens (420 mg + 4 mg/min for 45 minutes or 120 minutes) were investigated. These data showed that a molar ratio of more than 1.3:1 andexanet to total apixaban plasma concentration was needed to reverse anticoagulation as measured by anti-fXa activity (by 91-95%). This reversal directly correlated with the decrease in unbound fraction of apixaban, which decreased from 6.1% prior to andexanet administration to less than 0.5% at the end of the bolus infusion (a 92% decrease), demonstrating sequestration of the anticoagulant. Moreover, when a continuous (45-minute or 120-minute) infusion was added, the reversal of anti-fXa activity was maintained for the duration of the continuous infusion.

In the andexanet Phase 2 study where andexanet was administered to healthy human subjects who had been treated with rivaroxaban 20 mg PO QD, multiple cohorts of both andexanet bolus alone (210 mg, 420 mg, and 600 mg) and bolus + infusion regimens (720 mg + 4 mg/min for 120 minutes and 800 mg + 8 mg/min for 120 minutes) were investigated. The results showed that a 1.1 to 1.3:1 molar ratio of andexanet to total rivaroxaban plasma concentration was needed to reverse anticoagulation as measured by anti-fXa activity (average 76–81% decrease at the end of the bolus). This reversal directly correlated with the decrease in unbound fraction of rivaroxaban, which decreased from 24.5 ng/mL prior to andexanet administration to 5.1 ng/mL at the end of the bolus infusion (a 79.7% decrease), demonstrating sequestration of the anticoagulant. Moreover, when a continuous (120-minute) infusion was added, the reversal of anti-fXa activity was maintained for the duration of the continuous infusion. The change in dose from 420 mg used in the Phase 2 study to 400 mg in this study (14-505) and in the Phase 3 study (14-504) is due to the change in formulation and concentration of andexanet between the frozen formulation (3 mg/mL) and the lyophilized formulation (10 mg/mL).

Although in the controlled setting of a preclinical study, a bolus dose was sufficient to control bleeding to those levels seen in non-anticoagulated animals, the presentation of patients with acute major bleeds are likely to be variable. Therefore, the bolus with 2-hour infusion was chosen to allow sufficient time to allow for the hemostatic control.

3.4.5. Rationale for Re-dosing

In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated. For example, a patient might experience recurrent bleeding following andexanet infusion. Investigators will be required to document in the CRF the clinical justification (with objective criteria; see Section 6.2) for why subjects require additional dosing of andexanet. Re-dosing procedures will include laboratory sampling for anti-fXa activity and will commence at the "-00:15 to -00:01" step in the Schedule of Activities. Please refer to Appendix A for the detailed procedural requirements for re-dosed patients.

These decision criteria for re-dosing 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 patients or will be patients seen in the ED. As such, treatment with andexanet and subsequent monitoring will be done in a medical setting. It is expected that patients with acute major bleeding 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, and laboratory testing will be performed to monitor safety. After Study Day 1, patients will be followed for AEs through Study Day 3 and through the Follow-up Day 30 visit. Survival status will be ascertained on Study Days 1, 3, and 30 visits and cause of death will be recorded.

Antibody samples will be taken at baseline and Day 30 to assess immunogenicity against andexanet, FX, and FXa.

Additionally, although there have been no thrombotic events in any healthy subjects treated with andexanet in the Phase 1 or 2 studies, some prothrombotic markers (D-dimer, F1+2, and TAT) increase following andexanet infusion, generally resolving within 4 days after treatment. In this study, patients with TEs within 2 weeks, 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 and will be reported within 24 hours to the Sponsor.

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. In this study, severe and serious infusion reactions will be considered AEs of special interest and will be reported within 24 hours to the Sponsor.

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 possibility of antibody formation to andexanet, FX, or FXa, antibody testing will be performed at baseline and at the Study Day 30 visit. If antibodies to FX or FXa are detected for any patient, expedited reporting of the relevant finding(s) to regulatory authorities and investigators will occur.

The independent EAC, in addition to adjudicating the primary endpoint, will also adjudicate all re-bleeding events, potential TEs and deaths using pre-defined criteria as described in the Adjudication Charter. The 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. The main risk of anticoagulation with FXa inhibitors is uncontrolled bleeding. However, there are no available reversal agents for FXa inhibitors. Therefore, the need for such agents is currently an unmet need as the use of FXa inhibitors continues to increase. Patients enrolled in this study are those with an acute major bleeding episode in the setting of recent use of a FXa inhibitor. These bleeding episodes may be life-threatening, result in severe organ compromise, or prove fatal

without rapid control of bleeding and resuscitative measures. Andexanet may be beneficial in reversing anticoagulation and, thus, removing anticoagulation as a factor in the ongoing bleeding. In addition to any personal benefit to individual patients, there is a potential benefit to a growing number of patients treated with FXa inhibitors. 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 have emerged in studies of andexanet. However, whenever chronic anticoagulation is reversed in patients with an indication to receive it, risk of thrombotic events is increased. This risk must be balanced against the need to control the acute bleeding. The PD effect of andexanet is short. Therefore, shortly after the infusion is discontinued and once bleeding is controlled, it will be possible to return the patient to a therapeutically anticoagulated state as needed. It is recommended that the investigator carefully balance the risk of re-bleeding against the risk of a thrombotic event when considering whether to reinitiate anticoagulation for the patient.

The safety monitoring plan for this study is robust (see Section 3.6), 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 potential TEs by the EAC.

Based on the above considerations, the potential risks to patients in this study are justifiable. Patients or their proxies will be consented as to the potential risks and will be required to sign an 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

To be eligible for study enrollment study patients must satisfy the following inclusion criteria:

1. Either the patient or his or her medical proxy (or legally acceptable designee) has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening.
2. The patient must be at least 18 years old at the time of Screening.
3. The patient must have an acute overt major bleeding episode requiring urgent reversal of anticoagulation; acute major bleeding requiring urgent reversal of anticoagulation is defined by at least ONE of the following:
    - 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.
    - Acute overt bleeding associated with a fall in hemoglobin level by ≥ 2 g/dL, OR a Hgb ≤ 8 g/dL if no baseline Hgb is available.
    - Acute bleeding in a critical area or organ, such as pericardial, intracranial, or intraspinal.
4. The patient, for whom the bleeding is intracranial or intraspinal must have undergone a CT or MRI scan demonstrating the bleeding.
5. The patient received or is believed to have received one of the following within 18 hours prior to andexanet administration: apixaban, rivaroxaban, edoxaban, or enoxaparin (dose of enoxaparin ≥ 1 mg/kg/d).
6. For patients with ICH, there must be a reasonable expectation that andexanet treatment will commence within 2 hours of the baseline imaging evaluation.

4.2. Exclusion Criteria

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

1. The patient is scheduled to undergo surgery in less than 12 hours after end of andexanet infusion, with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes – see more examples in Appendix G).
2. A patient with ICH has any of the following:
    a. Glasgow coma score < 7.
    b. Estimated intracerebral hematoma volume > 60 cc as assessed by the CT or MRI.
3. Patients with visible, musculoskeletal, or intra-articular bleeding as the qualifying bleed.

4. The patient has an expected survival of less than 1 month.
5. The patient has a recent history (within 2 weeks) of a diagnosed Thrombotic Event (TE) as follows: Venous Thromboembolism (VTE; e.g., deep venous thrombosis, pulmonary embolism, cerebral venous thrombosis), myocardial infarction (including an isolated troponin elevation), disseminated intravascular coagulation (DIC), cerebral vascular accident, transient ischemic attack, unstable angina pectoris hospitalization, or severe peripheral vascular disease within 2 weeks prior to Screening (see Appendix E for DIC scoring algorithm).
6. The patient has severe sepsis or septic shock at the time of Screening (see definition Appendix F).
7. The patient is pregnant or a lactating female.
8. The patient has received any of the following drugs or blood products within 7 days or Screening:
    a. Vitamin K Antagonist (VKA) (e.g., warfarin).
    b. Dabigatran.
    c. Prothrombin Complex Concentrate products (PCC, e.g., Kcentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®).
    d. Whole blood, plasma fractions.
    e. Note: Administration of platelets or Packed Red Blood Cells (PRBCs) is not an exclusion criterion.
9. The patient was treated with an investigational drug < 30 days prior to Screening.
10. Planned administration of PCC, Fresh Frozen Plasma (FFP), or rfVIIa from Screening until within 12 hours after the end of the andexanet infusion.

4.3. 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.
- Withdrawal of consent. A patient may elect to withdraw consent to treatment or study participation at any time.

Patients who discontinue from the study after receiving any amount of andexanet should undergo all follow-up safety procedures, unless the patient also explicitly withdraws consent for these procedures, in which case they should undergo an Early Termination visit.

Reasons for all withdrawals/discontinuations of andexanet will be recorded.

4.4. Patient Replacement

Patients who discontinue prematurely will not be replaced. The study will continue to enroll patients until at least 162 patients have been enrolled who qualify for the Efficacy Analysis Population, of which at least 110 have ICH bleeds and at least 50 have high risk ICH bleeds. This may be accomplished by capping enrollment in other subgroups (e.g., patients with non-ICH bleeds).

4.5. Study Termination

Normal study termination is defined as the completion of all scheduled study visits, even if one or more interim visits or procedures was/were missed.

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.

5.1. Screening Period

5.1.1. Subject Identification Numbers

Patients will be considered to be in Screening, and be assigned an identification number, once they have signed the ICF. Patients will be considered to have enrolled in the study once they have received any amount of andexanet.

5.1.2. Visit Procedures (Days 1 to 30–37)

The visit procedures are described in the Schedule of Activities (Appendix A).

5.2. Unscheduled Visit

Additional clinical visits may be scheduled at the Investigators' 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.

5.3. Early Termination Visit

An early termination visit will be conducted if the patient is withdrawing 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.
- Obtain a local laboratory Complete Blood Count (CBC).
- Collect central laboratory specimens for thrombin generation and antibodies (anti-andexanet, anti-fX, anti-fXa, and neutralizing antibodies).

6.0 DRUG SUPPLIES AND DOSING

6.1. Formulation

Andexanet alfa (PRT064445) for Injection is supplied as either 50 mg/vial, 100 mg/vial, or 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 and contains 50 mg, 100 mg, or 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	**50 mg Vial**	**100 mg Vial**	**200 mg Vial**
Reconstitution Volume	**4.70 mL WFI**	**10.0 mL WFI**	**20.0 mL WFI**
Ingredients	**Quantity per Vial**		
Andexanet (PRT064445)	50 mg	100 mg	200 mg
Tris (Tromethamine)	6.1 mg	12.2 mg	24.4 mg
L-Arginine Hydrochloride	47.4 mg	94.8 mg	189.6 mg
Sucrose	100 mg	200 mg	400 mg
Mannitol	250 mg	500 mg	1,000 mg
Polysorbate 80	0.5 mg	1.0 mg	2.0 mg
Hydrochloric Acid	QS to pH 7.8 ± 0.3	QS to pH 7.8 ± 0.3	QS to pH 7.8 ± 0.3
Sterile Water For Injection	QS to 5 mL (removed during lyophilization process)	QS to 10 mL (removed during lyophilization process)	QS to 20 mL (removed during lyophilization process)

6.2. Dosing and Administration

Andexanet will be administered as an IV bolus, immediately followed by a continuous infusion. There are two possible dosing regimens as described below. Additional dosing regimens may apply when certain criteria are met. Re-dosed patients will undergo laboratory sampling procedures for anti-fXa activity that will commence at the "-00:15 to -00:01" step in the Schedule of Activities. Procedures are outlined in Appendix A.

Table 2: Dosing and Re-dosing Paradigms

Dose	Initial IV Bolus *	Follow-on IV Infusion *
Low Dose	400 mg at a target rate of 30 mg/min	4 mg/min for 120 minutes
High Dose	800 mg at a target rate of 30 mg/min	8 mg/min for 120 minutes

*** Criteria for Re-Treatment with Andexanet**

Consider re-dosing with andexanet (bolus + infusion; dose adjusted per dosing table) only if:

a) Bleeding recurs or occurs at a different anatomic site (as defined below) after initial andexanet bolus + infusion is completed, AND

b) Re-dosing initiation occurs within 24 hours after the end of the continuous andexanet infusion.

The investigator may consider re-dosing if a patient meets objective criteria for recurrent bleeding (or new bleeding at a different anatomic site) at any time up to 24 hours after completion of the initial andexanet bolus/infusion as follows:

- ICH:
  - Intracerebral hematoma: > 35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan.
  - Subarachnoid bleeding: > 35% increase in maximum thickness compared to baseline using the most dense area.
  - Subdural hematoma: > 35% increase in maximum thickness compared to baseline.
- Pericardial bleed. 10% or more increase in the size of pericardial effusion compared to baseline on repeat echocardiogram.
- Intra-spinal bleed. 10% or more increase in hematoma size on repeat CT or MRI scan compared to baseline.
- Gastrointestinal/genitourinary bleed. A > 20% decrease from baseline in both corrected hemoglobin and hematocrit, AND either: 1) hemodynamic compromise as evidenced by a sustained systolic blood pressure < 90 mmHg and a sustained heart rate > 120 bpm; OR 2) evidence of active bleeding visualized during an endoscopic or cystoscopic procedure.
- Other non-visible bleeding. 10% or more increase in hematoma size compared to baseline on repeat imaging, AND a > 20% decrease from baseline in both corrected hemoglobin and hematocrit.

The choice of low or high dose is based on the paradigm outlined in the following table. If a patient is re-dosed, the same paradigm should be followed.

Table 3: Andexanet Dose Regimens

FXa Inhibitor	FXa Inhibitor Last Dose	Timing of FXa Inhibitor Last Dose Before Andexanet Initiation	
		< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low Dose	Low Dose
	> 10 mg/ Unknown	High Dose	
Apixaban	≤ 5 mg	Low Dose	
	> 5 mg/ Unknown	High Dose	
Enoxaparin	≤ 40 mg	Low Dose	
	> 40 mg/ Unknown	High Dose	
Edoxaban	< 30 mg	Low Dose	
	≥ 30 mg/ Unknown	High Dose	
Unknown	Unknown	High Dose	

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 the date dispensed, dose dispensed, 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 Clinical Development 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 Pro-coagulant Treatments

7.2.1. Anticoagulants and Antiplatelet Drugs

Anticoagulant and antiplatelet drugs (including, but not limited to clopidogrel, aspirin, and Non-Steroidal Anti-Inflammatory Drugs [NSAIDs]) must be avoided from the signing of the ICF until after the 12-hour hemostatic efficacy evaluation measurements are made. Subsequently, it is recommended that investigators resume anticoagulation as soon as medically appropriate. If anticoagulation or an antiplatelet agent is restarted during the study, the date, time, and agent(s) used should be recorded on the Case Report Forms (CRFs).

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 a 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 number of units transfused should be recorded on the CRFs.

Pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, recombinant factor VIIa, rfVIIa, plasma, FFP) and whole blood should be avoided from the signing of the informed consent ICF until after the 12-hour hemostatic efficacy evaluation measurements are made, unless it is absolutely required for medical management of the patient. Use of these products will result in the patient being considered having poor/none hemostatic efficacy with andexanet.

Platelet transfusions may be administered according to standard institutional/local practices and/or guidelines.

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

Table 4: Use of Blood and Blood-related Products

Period	Any "PCC"	rFVII	FFP	Whole Blood	Platelets	PRBC
Pre-screening	No (7d)	No (7d)	No (7d)	No (7d)	Yes	Yes
Screening to 12 hours	No	No	No	Yes	Yes	Yes

7.2.3. Hemostatic Agents

Systemic anti-fibrinolytic (e.g., aminocaproic acid and tranexamic acid) and other systemic hemostatic agents may be administered according to standard institutional/local practices and/or guidelines.

Local hemostatic agents (e.g., microfibrillar collagen and chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) may be used as deemed clinically appropriate.

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

7.3. Diagnostic and Therapeutic Procedures for Bleeding

Patients scheduled to undergo surgery in < 12 hours are excluded from the study (see Section 4.2 Exclusion Criteria).

Minimally invasive procedures for diagnosis, management, or treatment of bleeding (e.g., gastrointestinal endoscopy, bronchoscopy, and central lines) may be performed as deemed clinically appropriate. The use of procedures for diagnosis and management of bleeding should be recorded on the CRFs.

7.4. Rescue Therapy

In this study, there is potential for patients to require additional andexanet treatment beyond what is stipulated. For example, a patient might experience re-bleeding, as defined by recurrent bleeding from the same or another anatomical site (or new bleeding from a different anatomical site) within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis, following andexanet infusion. Investigators will be required to document in the CRF the clinical justification for why subjects require additional dosing of andexanet. Re-dosing procedures will include laboratory sampling for anti-fXa activity and will commence at the "-00:15 to -00:01" step in the Schedule of Activities. Please refer to Appendix A for the detailed procedural requirements for re-dosed patients. These 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 1.4.5, 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 should be monitored carefully for signs and symptoms of thrombotic events throughout the course of the study. In the event that the Investigator suspects a thrombotic event, the appropriate evaluation should be performed (e.g., lower extremity ultrasound, pulmonary imaging), and resumption or escalation of anticoagulation should be considered.

9.0 ADVERSE EVENT REPORTING

9.1. Adverse Event Definitions

An AE is any undesirable event or any untoward medical occurrence that occurs to a participant during the course of a study, or the protocol-defined time after study termination, whether or not that event is considered study drug-related. A Treatment-Emergent AE (TEAE) is one that occurs following the receipt of any amount of study drug.

Examples of AEs include:

- Any treatment emergent signs and symptoms (events that are marked by a change from the patient's baseline/entry status [e.g., an increase in severity or frequency of pre-existing abnormality or disorder]).
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug.
- Apparently unrelated illnesses.
- Injuries or accidents.
- Extensions or exacerbations of symptomatology, subjective patient-reported events, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.
- Abnormal laboratory findings considered by the Investigator to be clinically significant, and that represent a worsening from baseline, should be reported as an AE. An abnormal laboratory value should be recorded as an AE if it:
    - Is associated with clinical signs or symptoms,
    - Requires an intervention,
    - Results in a serious AE, or
    - Results in study termination or interruption/discontinuation of study treatment.

When recording an AE resulting from a laboratory abnormality, the resulting medical condition, if known, rather than the abnormality itself should be recorded (e.g., record "anemia" rather than "low hemoglobin").

When a unifying diagnosis has been made that accounts for several possible signs and/or symptoms, the unifying diagnosis should be selected as the AE term. For example, the combination of general malaise, mild fever, headache, and rhinitis should be described as "upper respiratory syndrome" if this diagnosis has been made, rather than reporting the individual symptoms as separate events.

9.2. Serious Adverse Event Definition

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

- Results in 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. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned before the signing of the ICF, are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- 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.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. 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. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

9.3. Adverse Events of Special Interest

The following are AEs of special interest and should be reported as AEs (or as SAEs, if appropriate) within 24 hours after the Investigator is made aware of them, as described in Section 9.7:

- A thrombotic or embolic event of any severity
- Severe or serious infusion reaction

The investigator will assess relatedness of the AEOSI to andexanet as discussed in Section 9.4. In addition, the DSMB will periodically consider whether the occurrence of AEOSIs (whether related or not) warrant changes to the study (see Section 11.9 and DSMB Charter).

9.4. Assessment of Causal Relationship

The Investigator must separately determine the relationship of the event to the study drug. The causal association of AEs to study drug administration should be determined as follows: AEs that are considered to have a probable or possible relationship to treatment with study drug will be recorded as 'probable/possible,' while those that are considered to be unlikely or unrelated to treatment with study drug will be recorded as 'unlikely/unrelated.'

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, 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.

9.5. 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. Events that change severity during the course of follow-up should be recorded based on their highest severity grade.

Mild: awareness of sign or symptom but easily toleration.

Moderate: discomfort enough to cause interference with normal daily activities.

Severe: Inability to perform normal daily activities.

Life Threatening: Immediate risk of death from the reaction as it occurred.

9.6. Adverse Event Reporting

The AE reporting period starts with the signing of the ICF and continues through the Follow-up Day 30 visit. Survival status and reason for death will be ascertained at 12 hours and at the Day 3 and Follow-up Day 30 study visits.

Patients in this study 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 Study Day 30.

9.7. Reporting of Serious Adverse Events and Adverse Events of Special Interest

The SAE reporting period is the same as the AE reporting period (starts with the signing of the ICF and continues through the Follow-up Day 30 visit). All SAEs and AEs of special interest (see Section 9.3) must be reported by the Investigator by reporting the event on the appropriate CRF(s), within 24 hours from the point in time when the Investigator becomes aware of the SAE. Submission of an SAE should not be withheld even if complete information about the event is not available at the time of the initial report. Follow-up information on the SAE or AE of special interest should be sent promptly by the Investigator when any additional relevant information about the event becomes known to the Investigator, or as requested by Portola or its 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 factor X or factor Xa 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 IRB/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.

9.8. Pregnancy Reporting

If a woman who is a study patient becomes pregnant or a woman suspects she is pregnant from a male study patient, the Investigator should be informed immediately. Portola must, in turn, also be notified by the Investigator immediately by completing a Pregnancy Form. In the event a woman partner of a male patient is pregnant or suspects she is pregnant by the male patient, 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, stillbirth, pre-mature birth, or other outcome other than live normal birth, the Investigator should promptly report to the Sponsor the abnormal fetal outcome 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

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. Unbound Apixaban Plasma Levels

Plasma samples will be obtained at selected time points and analyzed for the concentration of unbound (and total) apixaban at a Central Laboratory. The assay for apixaban concentrations will be performed using validated Liquid Chromatography-Mass Spectrometry (LC-MS) methods. Unbound plasma concentrations for apixaban will be determined by equilibrium dialysis method. These assays will be performed at a Central Laboratory.

10.1.3. Unbound Rivaroxaban Plasma Levels

Plasma samples will be obtained at selected time points and analyzed for the concentration of unbound (and total) rivaroxaban. The assay for rivaroxaban concentrations will be performed using validated LCMS methods. Unbound plasma concentrations for rivaroxaban will be determined by equilibrium dialysis method. These assays will be performed at a Central Laboratory.

10.1.4. Unbound Edoxaban Plasma Levels

Plasma samples will be obtained at selected time points and analyzed for the concentration of unbound (and total) edoxaban. The assay for edoxaban concentrations will be performed using validated LCMS methods. Unbound plasma concentrations for edoxaban will be determined by equilibrium dialysis method. These assays will be performed at a Central Laboratory.

Of note, because enoxaparin is composed of a mixture of various molecular weights, there is no assay for measuring unbound enoxaparin levels.

10.1.5. 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 and non-TF-initiated thrombin generation assay. These assays will be performed at a Central Laboratory. Five parameters related to thrombin generation are measured: Endogenous Thrombin Potential (ETP), peak height, time to peak height, lag time, and velocity index. ETP is prospectively identified as the primary measure for thrombin generation.

10.1.6. Tissue Factor Pathway Inhibitor

TFPI (both total and free TFPI) will be measured using plasma samples in a Central Laboratory. Total TFPI level will be analyzed using an ELISA with polyclonal anti-TFPI antibodies. Free TFPI level will be analyzed using a monoclonal antibody specific to TFPI Kunitz-2 domain that binds to and inhibits FXa. Thus, the free TFPI level reflects the TFPI activity. TFPI results will be used to help assess the greater context of the state of coagulation post andexanet treatment.

10.1.7. Antithrombin III

ATIII antigen levels will be measured using plasma samples in a Central Laboratory. ATIII antigen levels will be analyzed using an ELISA with polyclonal antibodies. ATIII results will be used to help assess the greater context of the state of coagulation post andexanet treatment.

10.1.8. Anti-Factor IIa Activity

Anti-factor IIa activity levels will be measured in patients taking enoxaparin using plasma samples in a Central Laboratory. Anti-factor IIa activity will be measured using a modified chromogenic assay. Anti-factor IIa activity results will be used to more accurately evaluate the state of anticoagulation in patients taking enoxaparin.

10.2. Safety Assessments (other than Adverse Events)

10.2.1. Vital Signs

Vital signs include temperature, Blood Pressure (BP), Heart Rate (HR), and Respiratory Rate (RR).

10.2.2. Antibody Testing

Determination of the possible presence of antibodies to andexanet, FX (human), and FXa (human) will be done at specific time points using validated electrochemiluminescent methods.

For any sample that is positive for antibodies against andexanet, FX (human) or FXa (human), the potential for neutralizing antibody activity will be further assessed by measuring the functional activity in plasma. These tests will be performed by a Central Laboratory.

10.2.3. Clinical Laboratory Testing

Blood specimens for routine chemistry and hematology and other biomarkers will be obtained at selected time points (see Appendix A). The following assays will be performed at the Local Laboratory for inclusion criteria, clinical monitoring, and routine safety:

Hematology:	Hemoglobin, hematocrit, white blood cell (WBC), platelet count.
Coagulation:	International normalized ratio (INR).
Serum Chemistry:	Sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, calcium, phosphorus, and total, direct, and indirect bilirubin.
Serum or Urine Pregnancy Test:	In women

The following assays will be performed at a Central Laboratory:

Purpose	Assays
Critical Efficacy Assays	Anti-fXa activity Thrombin generation (TG) Anticoagulant free fraction (for direct FXa inhibitors)
Immunogenicity Assays	Antibodies to andexanet, FX, and FXa; neutralizing antibody (nAb) activity
Exploratory Efficacy Assays	Total and free TFPI ATIII antigen Anti-fIIa activity

11.0 STATISTICAL CONSIDERATIONS AND DATA ANALYSIS

The study objectives and study design are described in Section 2.0 and Section 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 (SAP).

11.1. General Considerations

It is anticipated that statistical summaries will be performed using SAS Version 9.2 (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 two-sided and reported at the 0.05 significance level. All CIs will be two-sided and reported at the 95% confidence level.

As part of their role, the EAC is tasked to determine whether there is sufficient information available to make a valid assessment. If the case is adjudicated by the Committee as non-assessable, it will be further classified as non-evaluable due to administrative reasons (e.g., follow-up scan not available) or non-evaluable due to clinical reasons (e.g., patient died). The criteria for which a subject may be rendered non-evaluable for hemostatic efficacy will be further specified in the Adjudication Charter.

Both primary objectives will be assessed using patients who have a baseline anti-fXa level at or above the evaluability threshold (75 ng/mL for apixaban and rivaroxaban, 40 ng/mL for edoxaban, 0.25 IU/mL for enoxaparin). A supportive analysis will examine the same endpoints in patients who have a baseline anti-fXa level of less than the threshold value. Another supportive analysis will assess all patients, with stratification by baseline anti-fXa level of at least or less than the threshold value.

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. Safety Analysis Population

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

11.3.2. Efficacy Analysis Populations

The Efficacy Analysis Population will include all enrolled patients who: 1) receive any amount of andexanet treatment; 2) are determined by the EAC to meet the bleeding entry criteria; and 3) have a baseline anti-fXa level of at least 75 ng/mL for patients receiving apixaban and rivaroxaban, 40 ng/mL for patients receiving edoxaban, and 0.25 IU/mL for patients receiving enoxaparin. Additional efficacy analysis populations may be defined in the SAP.

11.4. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized for both the safety and efficacy populations. 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

For anti-fXa activity level-related efficacy endpoints, the baseline measurement will be the last value obtained prior to the start of the andexanet bolus. The evaluation period for anti-fXa activity covers the period of time from 5 minutes following the end of the andexanet bolus to 10 minutes after the end of the andexanet infusion. Hemostatic efficacy will be assessed from baseline through the 12 hour time point after the end of the andexanet infusion. As with anti-fXa activity, baseline is defined as the last assessment prior to the start of the andexanet bolus. Prior to assessment of hemostatic efficacy, the EAC will determine whether the patient meets bleeding entry criteria and whether the hemostatic efficacy is evaluable (i.e., if sufficient clinical data, such as hemoglobin and/or imaging results, are available to assess efficacy). The EAC will categorize the hemostatic response as excellent, good, poor/none, or non-evaluable based on the pre-specified definitions in Appendix B and Section 11.1. Re-bleeding episodes will also be evaluated by the EAC according to the following definition: bleeding (whether from the same anatomical site or from a different anatomic site) in patients within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis. If a patient is re-dosed with andexanet due to re-bleeding up through the 12 hour time point, the patient will be considered to have poor/none hemostatic efficacy.

11.5.2. Primary Efficacy Endpoints

The two primary endpoints are the following:

> The percent change from baseline in anti-fXa activity to the nadir from the evaluation period (where the evaluation period starts 5 minutes following the end of the andexanet bolus and ends 10 minutes after the end of the andexanet infusion),

AND

> The achievement of hemostatic efficacy.

The primary endpoints, including the evaluation of hemostatic efficacy in specific study populations against specific comparators, will be ordered in a fixed sequence multiple comparisons (i.e., hierarchical) fashion as delineated in the SAP.

11.5.3. Secondary Efficacy Endpoint

The secondary objective is to assess the relationship between the two primary endpoints to establish change in anti-fXa activity as a predictor of achievement of hemostatic efficacy. No additional endpoint is defined to support this objective.

11.5.4. Exploratory Efficacy Endpoints

The following additional efficacy endpoints will be analyzed as exploratory:

- The number of patients receiving one or more red blood cell transfusions from the start of the andexanet bolus through 12 hours after the end of andexanet infusion.
- For patients receiving apixaban, rivaroxaban, or edoxaban, to evaluate the decrease in free fraction of the FXa inhibitor following andexanet administration.
- The number of red blood cell units transfused per patient from the start of the andexanet bolus through 12 hours after the end of the andexanet infusion.
- The use of non-study-prescribed blood products and/or hemostatic agents.
- The occurrence of re-bleeding following andexanet treatment. Re-bleeding is defined as follows: recurrent bleeding from the same or another anatomical site, or new bleeding from a different anatomical site within 24 hours of initial andexanet treatment and after achieving initial good/excellent hemostasis.
- Andexanet reversal of anticoagulant effect as measured through TG parameters (with, Endogenous Thrombin Potential [ETP] as the primary measure), for both the Tissue Factor (TF)-initiated assay and the non-TF-initiated assay.
- TFPI levels, both free and total, pre- and post-administration of andexanet.
- ATIII levels, pre- and post-administration of andexanet.
- Anti-factor IIa levels, pre- and post-administration of andexanet (enoxaparin patients only).
- The achievement of hemostatic efficacy in ICH patients at high risk of hematoma expansion.
- Change from baseline in GCS at 1 hour, 12 hours, and 30 days (for ICH patients only).
- Change from baseline in mRS at 1 hour, 12 hours, and 30 days (for ICH patients only).
- Change from baseline in NIHSS at 1 hour, 12 hours, and 30 days (for ICH patients only).

11.5.5. Safety Endpoints

- AEs, vital signs, and clinical laboratory measurements
- Centrally-adjudicated TEs and deaths
- Antibodies to andexanet, FX, and FXa

11.5.6. Statistical Methodology for Endpoint Analyses

The first primary efficacy endpoint, i.e., percent change in anti-fXa activity from baseline (last measurement before administration of andexanet) to nadir (the lowest level measured between 5 minutes prior to the start of andexanet administration and 10 minutes after the end of the andexanet administration) will be calculated for each patient as change = 100 %×(post-baseline)/baseline. Percent change from baseline in anti-fXa activity will be assessed with two-sided 95% CIs. A nonparametric CI for the median will be reported. If the nonparametric CI for the median excludes 0, the first primary objective will be considered to have been met. For the first primary endpoint, patients who do not have at least one anti-fXa activity level within the evaluation period for non-administrative reasons will have percent decrease imputed as 0.0% (i.e., using the baseline value as the nadir value).

The second primary efficacy endpoint, proportion of efficacy evaluable patients who are adjudicated to have effective hemostasis (excellent or good) by the independent EAC will be summarized as a point estimate with an asymptotic 95% confidence interval.

To maintain the type I error rate, the statistical evaluation of the primary endpoints, including the analysis of hemostatic efficacy in specific study populations against specific comparators, will be ordered in a fixed sequence multiple comparisons (hierarchical) procedure.

The secondary endpoint will be assessed by plotting the Receiver Operating Characteristics (ROC) curve and calculating the Area Under the Curve (AUC). Patients will be classified as success or failure based on achievement of hemostatic efficacy. For each potential cut point of a percent change in anti-fXa activity, the sensitivity and specificity of that cut point to distinguish achievement of hemostatic efficacy will be calculated. The ROC plots sensitivity by 1 - specificity. An AUC of 0.5 or lower indicates that the percent change in anti-fXa activity does not predict achievement of hemostatic efficacy. An AUC of 0.7 or higher is indicative of a relationship that is more useful in predicting hemostatic efficacy [27]. The Minimum Clinically Important Difference (MCID) of percent decrease in anti-fXa activity will be derived as the value that simultaneously maximizes sensitivity and specificity.

Exploratory endpoints consisting of counts data will be summarized by observed rates and exact 95% CIs. Dichotomous data will be described analogously to the primary endpoint.

Further details of the analysis of the efficacy endpoints will be provided in the SAP.

11.5.7. Assessment of the Relationship Between Effective Hemostasis and Percent Decrease in Anti-fXa Activity

The following analyses are planned to further assess the relationship between hemostasis and decrease in anti-fXa activity:

Analysis of "Responders" (patients with a large percent decrease in anti-fXa activity) anchored to Hemostatic Efficacy. The percent decrease from baseline in anti-fXa activity in the evaluation period (relative to baseline) will be anchored to the achievement of hemostatic efficacy (i.e., the primary endpoint). This will be done calculating the median and mean percent decrease from baseline values for patients who achieved hemostatic efficacy and for patients who did not achieve hemostatic efficacy, with the expectation that those patients who achieved hemostatic efficacy had a greater mean and median percent decrease than those who did not.

Cumulative Distribution Function (CDF) Analysis. The CDF of change in anti-fXa activity for patients with and without benefit will be plotted. The horizontal axis will be the anti-fXa activity achieved (from 0-100%, and including negative values if any patient had an increase in anti-fXa activity), and the vertical axis will be the percent of patients with that level, or less, achieved. The two CDFs will be plotted on the same figure to allow comparisons. This enables visualization of percent with clinical benefit at every possible cut-point of percent decrease in anti-fXa activity.

In addition, other analyses will be performed, allowing for adjustment of potentially confounding variables. Variables that may confound evaluation of a correlation between reversal of anti-fXa activity with effective hemostasis include anatomical location of bleeding, mechanism of injury (e.g., blunt vs. penetrating trauma; traumatic vs. spontaneous), severity of injury, severity of bleeding, presence and timing of interventions to stop bleeding (e.g., endoscopic cautery of bleeding ulcers, surgical ligation of bleeding vessel), and use of coagulation or hemostatic factors. Assessment of various parameters of prediction of clinical hemostasis will also be considered, including a threshold of anti-fXa activity, a percent reduction in anti-fXa activity, and an absolute reduction in anti-fXa activity.

11.6. Determination of Sample Size

The initial sample size is based on the second primary efficacy variable. A sample size of 162 efficacy evaluable patients will provide 80% power for a two-sided 95% CI that is completely above 50% for the second primary efficacy variable of effective hemostasis, demonstrating a response rate above 50% for that variable. This is based on an anticipated response rate of 61%. Further details on the sample size calculation are provided in the SAP.

The power to demonstrate a decrease in anti-fXa activity is expected to be higher than that to demonstrate a change in hemostatic efficacy. In prior studies in healthy normal subjects, the mean percent change in anti-fXa activity was -93.9 with a standard deviation of 1.7 within 5 minutes of the end of the administration of a bolus of andexanet, compared to -20.7 (8.6) within 5 minutes of the end of the administration of a bolus of placebo, among subjects who had received apixaban dosed to steady state. With 162 patients in the Efficacy Analysis Population with baseline anti-fXa activity of at least 75 ng/mL for patients receiving apixaban and rivaroxaban, 40 ng/mL for patients receiving edoxaban, and 0.25 IU/mL for patients receiving enoxaparin, the power to demonstrate that the true percent change is less than 0 is over 99%.

It is estimated that approximately 30% of the andexanet-treated patients will have pre-andexanet anti-fXa activity of < 75 ng/mL for patients receiving apixaban and rivaroxaban, < 40 ng/mL for patients receiving edoxaban, and 0.25 IU/mL for patients receiving enoxaparin, and therefore these patients will not be included in the primary analysis. Additionally, it is estimated that up to 5% of patients will be unevaluable for reasons unrelated to andexanet. In addition, enrollment will continue until at least 110 evaluable ICH patients (50 of whom are deemed to be high risk) are enrolled to more comprehensively capture clinical outcomes in this high risk patient population. Therefore, it is anticipated that up to 250 patients may have to be treated to achieve the requisite number of evaluable patients.

The sample size may be adjusted based on changes in enrollment strategy for various bleed types and other subgroups (e.g., FXa inhibitor), a need to meet regulatory requirements for sufficient numbers of patients for each FXa inhibitor and/or geographic region, or new information from registries, observational studies, clinical trials, and/or other sources. Details of these adjustments, if performed, will be provided in the SAP. To accommodate a potential increase in sample size based on these factors, the total enrollment will be approximately 500 patients.

The sample size and power computations were performed using the software package PASS 14 (Version 14.0.8, NCSS, LLC, Kaysville, Utah, USA).

11.7. Safety Endpoints and Summaries

11.7.1. Adverse Events

Safety will be assessed by examination of survival status, AEs (including central adjudication of TEs and deaths), vital signs, clinical laboratory measurements, thrombin generation, TFPI levels, antibodies to andexanet, FX, and FXa.

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.

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

Treatment-Emergent Adverse Events (TEAEs), including preferred terms defined by the Medical Dictionary for Regulatory Activities (MedDRA), will be summarized by system organ class. Arterial and venous thrombotic events and serious and severe infusion reactions, considered AEs of special interest, will be separately summarized.

The number of events, the number of patients, and the percentage of patients who experienced at least one TEAE will be presented. 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.

Concomitant medications will be coded using the WHO Drug Dictionary.

11.7.2. Thrombotic Events

All potential thrombotic events will be assessed by the EAC and summarized descriptively, including whether patients were re-anticoagulated prior to event. The Investigator will determine whether a TE is attributable to andexanet, while the DSMB will determine whether the occurrence of TEs in aggregate (related or not) warrant changes to the study.

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, CV procedures, CV hemorrhage, and other CV causes) will be classified as related to bleeding or non-hemorrhagic.

11.7.4. Laboratory Parameters

Clinical laboratory parameters including hematology, chemistry, and coagulation markers (e.g., anti-fXa activity and thrombin generation) will be summarized by time point.

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

Shift tables of chemistry, hematology, and coagulation markers will be used to summarize change from baseline to post-baseline time points.

11.8. Subgroup Analyses

Consistency of efficacy across important subgroups will be investigated.

In addition to the above analyses, primary efficacy and safety will be summarized, at a minimum, for the following subgroups: sex (male, female), race (any race with at least 5 members, all others combined), age (< 65 years, ≥ 65 years, ≥ 75 years), anticoagulant, type of bleed (e.g., ICH vs. GI vs. other), and requirement for re-dosing. In addition, hemostatic efficacy in ICH patients at higher risk for hematoma expansion will be evaluated as an exploratory efficacy analysis. Patients at higher risk for hematoma expansion will be defined by the following criteria:

For intracerebral/intraparenchymal bleeding, volume of hematoma > 3 mL, OR

For subdural bleeding, thickness of hematoma > 10 mm or midline shift > 5 mm, OR

For subarachnoid bleeding, thickness of hematoma > 10 mm.

A minimum of 50 efficacy evaluable patients meeting these criteria, as determined by the core lab, will be enrolled in this subgroup.

Screening for differential treatment effects on the primary endpoints across subgroups will be conducted using a formal test of interaction obtained from a logistic regression model.

11.9. Interim Analyses

It is anticipated that data from this study will be summarized at least one time before the completion of the study, to provide information on accumulating safety and efficacy of andexanet. Such summaries will be provided to support regulatory review or commercial use after the product is commercially available, with justification provided for each summary. These summaries will not be used to alter the ongoing study or to change any aspect of the design or conduct of the study, and no adjustment to the type I error rate or confidence interval coverage will be made to account for these summaries. An informal assessment of hemostatic efficacy and baseline and demographic characteristics will be presented to investigate whether patients enrolled after the interim summaries are different from patients enrolled prior to the interim summaries or have different outcomes, to assess the potential for the interim summaries to induce bias.

Interim summaries of safety data will be performed periodically at a minimum frequency of once a year in order to report safety data from the ongoing study. The DSMB will meet regularly to review accumulating safety data.

Summaries of baseline characteristics will be reported during the trial. The inclusion/exclusion criteria may be changed during the study based on the accumulating data. For example, the time requirement for taking the FXa inhibitor—within 18 hours prior to study enrollment—may be changed if anti-fXa levels are not sufficiently high in patients who report having taken FXa inhibitors at a substantial time (e.g., more than 12 hours) before enrolling in the study.

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 the inclusion criteria and primary efficacy endpoint and potential TEs (for safety) for all patients.
- Independent DSMB: Monitoring of all safety data.
- Executive Committee: Oversight of study conduct and publication(s) of study data.
- Steering Committee: Assessment and management of country-specific or region-specific issues and activities.

13.0 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

13.1. Institutional Review Board or Independent Ethics Committee

The protocol and informed consent 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, International Conference on Harmonisation, 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 are allowed. Note: When the consent cannot be obtained from the patient or proxy, the decision to treat due to the emergent nature of the situation can be made by the attending physician. (This pertains only to specific countries and/or jurisdictions where laws explicitly allow it.)

13.3. Supplementary Documentation

Before initiation of the study, 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 Reporting and Case Report Forms

Data for each patient will be entered into the CRF and verified by the Investigator. It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported on the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient's clinical status.

The Investigator or designated representative should complete the CRF as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. CRF data will be processed in a US 21 Code of Federal Regulations (CFR) Part 11-compliant system.

13.5. Retention of Data

Sites are required to adhere to the document retention requirements set forth by the United States FDA in addition to local requirements set forth by their respective country/regional regulatory authorities. U.S. Federal regulations require that a copy of records (e.g., laboratory data slips, source documents, test article disbursement records), which support case records of this study, must be retained in the files of the responsible Investigator for a minimum of 2 years after notification by the Sponsor that the FDA has approved a marketing application for the drug and indication being investigated, or the investigation has been terminated.

ICH E6 *Good Clinical Practice* requires the IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

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. Any other changes or deviations 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. Certain deviations relating to missed assessment (for reasons other than patient death) that render a subject non-evaluable for key analysis will be considered significant deviations.

13.7. Study Monitoring

The Investigator will allow representatives of Portola Pharmaceuticals, Inc. to periodically audit (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.

13.8. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates andexanet was received from Portola and dispensed to the patients, 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 designated depot of Portola Pharmaceuticals, Inc. after written authorization is obtained from Portola. 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. 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.

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15.0 LIST OF APPENDICES

Appendix A: Schedule of Activities

Appendix B: Rating System for Effective Hemostasis

Appendix C: Glasgow Coma Scale (GCS)

Appendix D: Modified Rankin Score (mRS)

Appendix E: Disseminated Intravascular Coagulation (DIC) Scoring Algorithm

Appendix F: Definitions of Severe Sepsis and Septic Shock

Appendix G: Examples of Minor Procedures Allowed

Appendix H: National Institutes of Health Stroke Scale (NIHSS)

Appendix I: Protocol Summary of Changes (Amendment 5 vs Amendment 6)

APPENDIX A. SCHEDULE OF ACTIVITIES

Study Day	**1**										**2**	**3**		**30**[12]
Study Hour and Time Window	**-3:00 to -00:01**	**-00:15 to -00:01**	**00:00 to EOB** (15-30 min)	**EOB to EI** (120 min) **EOB +30 min**	**EOB to EI** (120 min) **EI -30 min**	**EI + 1 hr +/- 30 min**	**EI + 4 hrs +/- 30 min**	**EI + 8 hrs +/- 90 min**	**EI + 12 hrs +/- 1 hour**	**EI + 18 hrs +/- 1 hour**	**EI + 24 hrs +/- 1 hour**	**EI + 48 hrs +/- 2 hour**	**EI + 72 hrs +/- 6 hour**	**+7 d**
Obtain Consent [1]	X													
Determine Eligibility	X													
Obtain Medical History [2]	X													
Obtain Prior Medications [2] [13]	X													
Weight [3]	X													
Vital Signs (BP, HR, RR, temp)	X	X		X	X	X	X	X	X					
Local Labs: INR	X													
Local Labs: Chemistry & pregnancy test [4]	X													
Local Labs: CBC		X							X					
Critical Efficacy Central Labs: Anti-fXa activity unbound anticoagulant		[9] [14] X		[9] [14] X	[9] [14] X		X	X	X					
Critical Efficacy Central Labs: Thrombin Generation	X			X [11]	X [11]		X	X	X	X	X	X	X	X
Critical Immunogenicity Central Labs: Antibodies to andexanet, FX, FXa nAb (andexanet) nAb (FX/FXa)	X													X
Exploratory Efficacy Central Labs: TFPI Panel & ATIII	X				X		X	X	X		X	X	X	X

Study Day	**1**										**2**	**3**		**30**[12]
Study Hour and Time Window	**-3:00 to -00:01**	**-00:15 to -00:01**	**00:00 to EOB** (15-30 min)	**EOB to EI** (120 min) **EOB +30 min**	**EI -30 min**	**EI + 1 hr +/- 30 min**	**EI + 4 hrs +/- 30 min**	**EI + 8 hrs +/- 90 min**	**EI + 12 hrs +/- 1 hour**	**EI + 18 hrs +/- 1 hour**	**EI + 24 hrs +/- 1 hour**	**EI + 48 hrs +/- 2 hour**	**EI + 72 hrs +/- 6 hour**	**+7 d**
Administer andexanet bolus, immediately followed by an infusion			**Bolus**	**Infusion**										
Echocardiogram Pericardial Bleeds	X								X					
CT or MRI (e.g., ICH and intra-spinal) [5]	X [10]					X			X					X
Glasgow Coma score (ICH patients only)	X					X			X					X
Modified Rankin score (ICH patients only)	X					X			X					X
NIH Stroke Scale (ICH patients only) (Appendix H)		X				X			X					X
Record blood products and hemostatic treatments [6]		X												
Record bleeding-related diagnostic and therapeutic procedures [7]		X												
Record volume of colloid and crystalloid [6]		X												

Study Day	1										2	3		30[12]
Study Hour and Time Window	-3:00 to -00:01	-00:15 to -00:01	00:00 to EOB (15-30 min)	EOB to EI (120 min) EOB +30 min	EOB to EI (120 min) EI -30 min	EI + 1 hr +/- 30 min	EI + 4 hrs +/- 30 min	EI + 8 hrs +/- 90 min	EI + 12 hrs +/- 1 hour	EI + 18 hrs +/- 1 hour	EI + 24 hrs +/- 1 hour	EI + 48 hrs +/- 2 hour	EI + 72 hrs +/- 6 hour	+7 d
Record hours in ED, ICU/critical care, general hospital floor, and as an inpatient [8]		X												
Record Adverse Events (AE)	X	X								X	X	X	X	X
Record Concomitant Medications [13]		X											X	X
Ascertain Survival Status		X											X	X

BP = Blood pressure; CBC = Complete blood count; CT = Computed tomography; ED = Emergency department; EI = End of infusion; EOB = End of bolus; FX = Factor X; FXa = Activated factor X; HR = Heart rate; ICH = Intracranial hemorrhage; ICU = Intensive care unit; INR = International normalized ratio; MRI = Magnetic Resonance Imaging; nAb = Neutralizing antibody (activity); RR = Respiratory rate; Temp = Temperature

[1] Unless exception for informed consent for emergency procedures has been obtained.

[2] Obtain as much of a full medical history and list of medications as feasible prior to initiation of study-specific procedures.

[3] If not possible to measure weight, a reported weight or recent weight from the medical record is acceptable.

[4] Pregnancy test in females under 55 years only; test may be done on urine or serum.

[5] Perform CT or MRI at baseline and EI + 12 hours. For ICH patients, the 1 hour scan is required, and should be as close to 1 hour following the EI. (Scans performed greater than 4 hours *after* the end of infusion are considered out of window).

[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. For ICH, this should include CT or MRI scan; for pericardial, an echocardiogram; and for intra-spinal a CT or MRI should be performed.

[8] Record through hospital discharge.

[9] This qualitative assay will be performed at baseline to determine which anti-fXa (apixaban, edoxaban, enoxaparin, or rivaroxaban) is present.

[10] **It must be reasonably expected that the CT or MRI can be performed within 2 hours of the start of andexanet administration to avoid hematoma expansion prior to dosing.** Data from the head CT or MRI done to confirm the diagnosis or establish the extent of ICH (or Intra-spinal bleed) will be recorded.

[11] Samples for anti-fXa activity and unbound anticoagulant should be drawn at two time points; one at (or within 30 minutes after) the end of the bolus, and another at (or within 30 minutes prior to) the end of the infusion.

[12] Window: Days 30–37. Patients who discontinue from the study after receiving any amount of andexanet but before this visit should undergo all follow-up safety procedures, unless the patient also explicitly withdraws consent for these procedures, in which case they should undergo an Early Termination visit.

[13] Record dates of use of anticoagulant(s) on the anticoagulant CRF.

[14] **Laboratory sampling procedures required for re-dosed patients pertain to anti-fXa activity only.**

APPENDIX B. RATING SYSTEM FOR EFFECTIVE HEMOSTASIS

Excellent [1] (effective)	○ ICH: • Intracerebral hemorrhage: ≤ 20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at both the 1 and 12 hour post infusion time points. • Subarachnoid bleeding: ≤ 20% increase in maximum thickness using the most dense area on the follow-up vs. baseline at both the 1 and 12 hour post infusion time points. • Subdural hematoma: ≤ 20% increase in maximum thickness at both the 1 and 12 hour post infusion assessments compared to baseline. • Pericardial bleed. No increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion. • Intra-spinal bleed. No increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion. • Other (e.g., gastrointestinal bleeding, genitourinary bleeding): ≤ 10% decrease in both corrected hemoglobin/hematocrit at 12 hours [2,3] compared to baseline.
Good [4] (effective)	○ ICH: • Intracerebral hematoma: > 20% but ≤ 35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at +12-hour time point. • Subarachnoid bleeding: > 20% but < 35% increase in maximum thickness using the most dense area on the follow-up at +12 hours vs. baseline. • Subdural hematoma: > 20% but < 35% increase in maximum thickness at +12 hours compared to baseline. • Pericardial bleed. < 10% increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion. • Intra-spinal bleed. < 10% increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion. • Other: > 10% to ≤ 20% decrease in both corrected hemoglobin/hematocrit at 12 hours compared to baseline.[2,3]

Poor/None [5] (not effective)	○ ICH: • Intracerebral hematoma: > 35% increase in hematoma volume on a CT or MRI compared to baseline on a repeat CT or MRI scan at +12-hour time point. • Subarachnoid bleeding: > 35% increase in maximum thickness using the most dense area on the +12 hours vs. at baseline. • Subdural hematoma: > 35% increase in maximum thickness at +12 hours compared to baseline. • Pericardial bleed. 10% or more increase in the size of pericardial effusion on repeat echocardiogram done within 12 hours of the end of infusion. • Intra-spinal bleed. 10% or more increase in hematoma size on repeat CT or MRI scan done within 12 hours of the end of infusion. • Other: > 20% decrease in both corrected hemoglobin/hematocrit.[2,3]

[1] For all types of bleeding: no additional plasma, blood products (whole blood products not including packed red blood cells [PRBCs]) and/or coagulation factor products required after initial treatment with andexanet.

[2] The smallest percentage decrease in hemoglobin or hematocrit should be used to determine the efficacy rating of excellent, good, or poor/none. The net change is defined as the difference between the corrected hemoglobin or hematocrit value at baseline and 12 hours after infusion.

[3] For the adjusted hemoglobin and hematocrit calculation, it will be assumed that for each unit of PRBC transfusion there is an increase of 1 g/dL in hemoglobin and a 3% increase in hematocrit.

[4] For all types of bleeding, no more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. "Blood products" include whole blood but not PRBCs.

[5] For all types of bleeding, more than two additional units of plasma or blood products and/or coagulation factor products required after initial treatment with andexanet. "Blood products" include whole blood but not PRBCs.

APPENDIX C. GLASGOW COMA SCALE (GCS)

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

NT = Not testable

APPENDIX D. MODIFIED RANKIN SCORE (MRS)

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention
6	Dead

APPENDIX E. DISSEMINATED INTRAVASCULAR COAGULATION (DIC) SCORING ALGORITHM [28]

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

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.

APPENDIX F. DEFINITIONS OF SEVERE SEPSIS AND SEPTIC SHOCK [29]

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 Limits of laboratory Normal (ULN)
- Urine output < 0.5 mL/kg/hr for more than two hours despite adequate fluid resuscitation
- Acute lung injury with PaO_2/FIO_2 < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FIO_2 < 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 systolic blood pressure (SBP) < 90 mmHg, or Mean Arterial Pressure (MAP) < 70 mmHg, or a SBP decrease > 40 mmHg, or less than two 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 G. EXAMPLES OF MINOR PROCEDURES ALLOWED

- Burr holes (trepanation)
- Arthroscopy
- Thoracentesis
- Pericardial puncture/drainage
- Embolization
- Endoscopy with cauterization/embolization
- Cystoscopy
- Laparocentesis
- Lumbar puncture
- Colonoscopy
- Radiofrequency ablation of coronary isthmus
- Angiography
- Cardiac catheterization
- CT-guided abscess drainage
- Knee arthrocentesis

APPENDIX H. NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert**; but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert**; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

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NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

_____

_____

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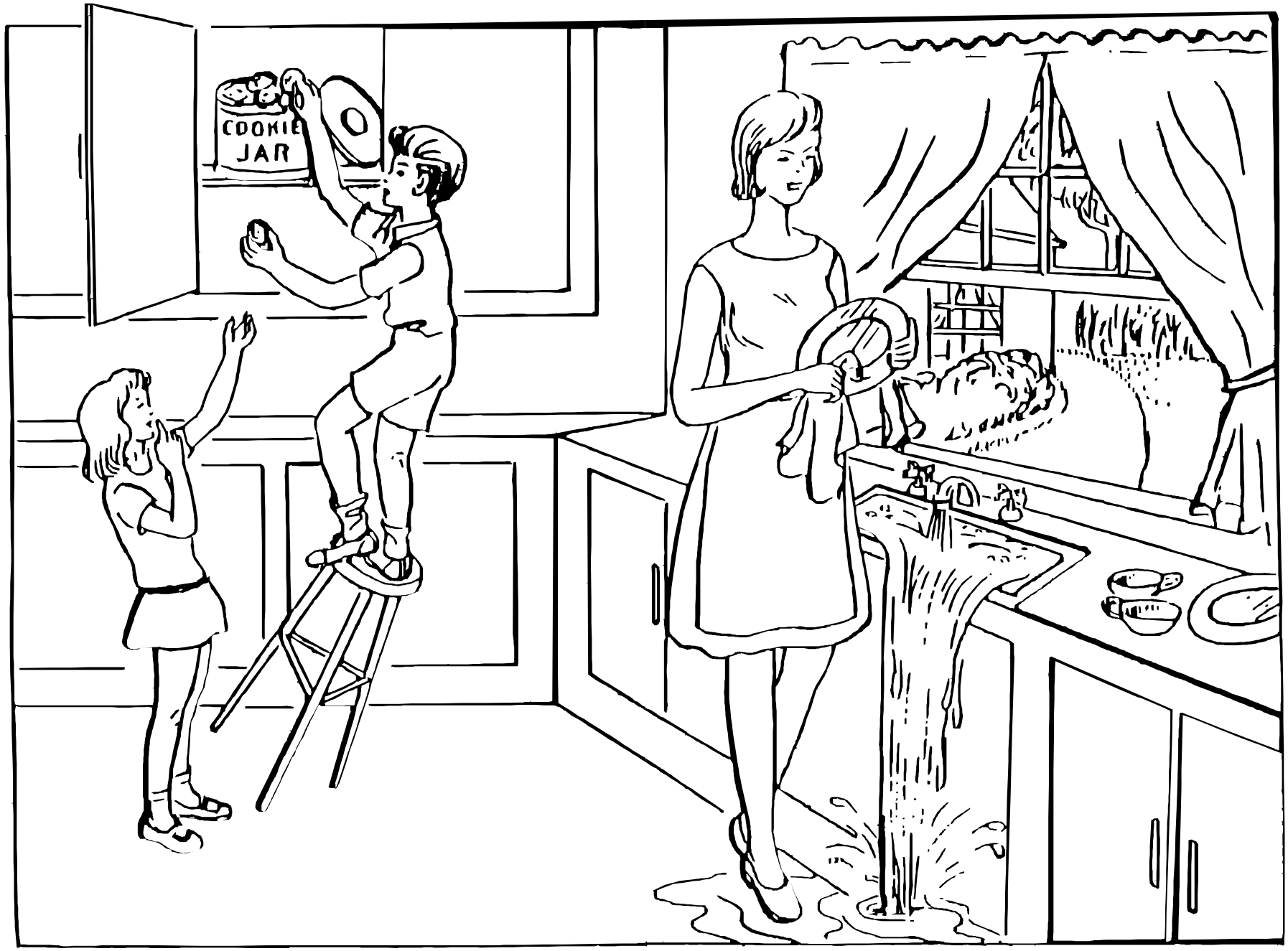

COOKIE
JAR

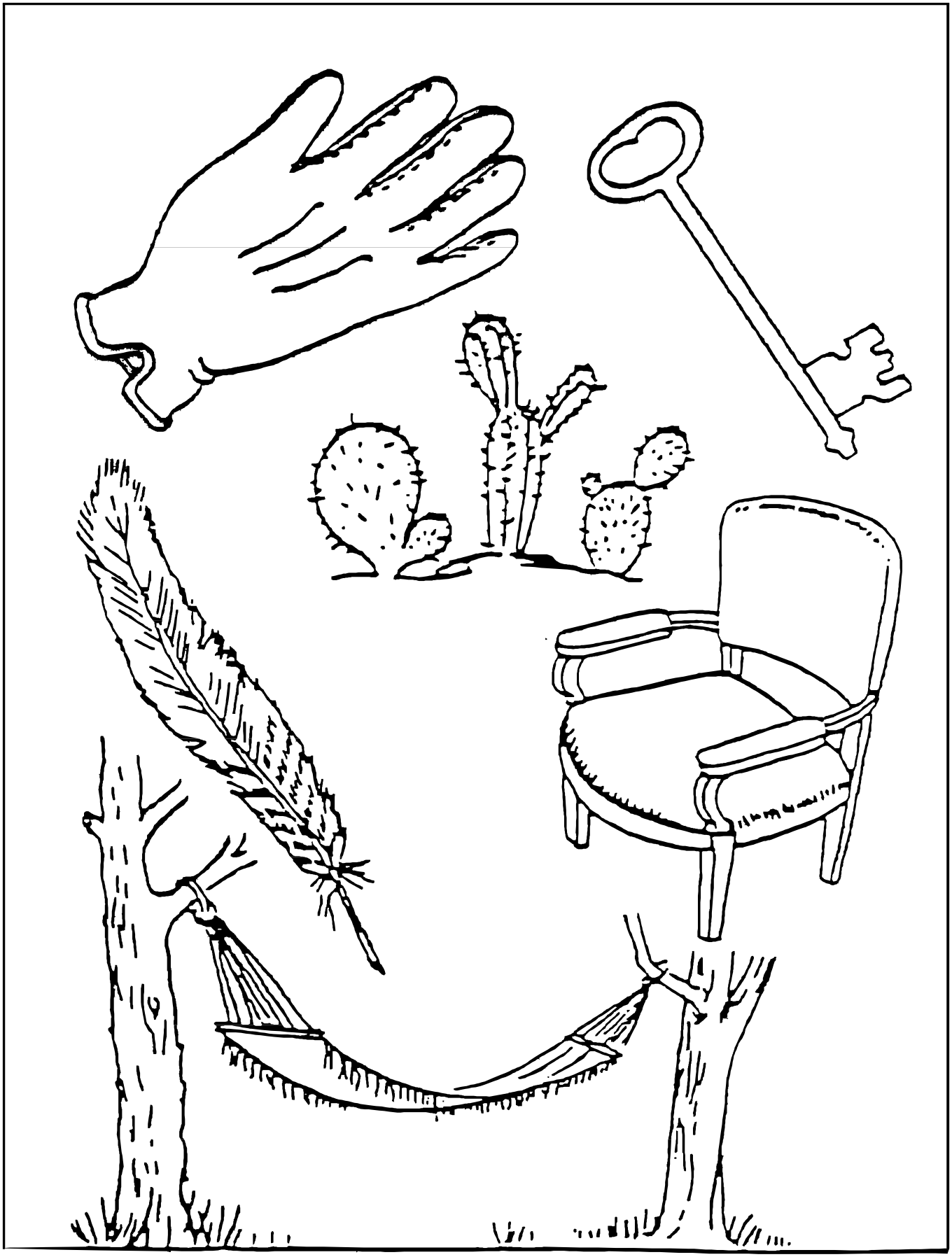
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

APPENDIX I. PROTOCOL SUMMARY OF CHANGES (AMENDMENT 5 VS AMENDMENT 6)

First Section of Occurrence (& throughout document)	Old Text (from Amendment 5)	New Text (strikethrough indicates deleted text / bold italics indicates added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
Synopsis (Study Design)	Patients will be evaluated for the primary hemostatic efficacy endpoints for 12 hours from the end of andexanet infusion with clinical and imaging assessments for bleeding: head Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), Glasgow Coma Scale (GCS), modified Rankin Score (mRS), and National Institutes of Health Stroke Score (NIHSS) (Appendix H) for Intracranial Hemorrhage (ICH); transfusion corrected hemoglobin and hematocrit for non-visible bleeding; echocardiogram for pericardial bleed; and ultrasound or CT/MRI scan for intraspinal bleeding.	Patients will be evaluated for the primary hemostatic efficacy endpoints for 12 hours from the end of andexanet infusion with clinical and imaging assessments for bleeding: head Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), Glasgow Coma Scale (GCS), modified Rankin Score (mRS), and National Institutes of Health Stroke Score (NIHSS) (Appendix H) for Intracranial Hemorrhage (ICH); transfusion corrected hemoglobin and hematocrit for non-visible bleeding; echocardiogram for pericardial bleed; and ~~ultrasound or~~ CT/MRI scan for intraspinal bleeding.	This was an error in the Synopsis. Updated for accuracy and to align with the protocol body.	NS
1.2 Description of Andexanet	In addition to reversal of FXa activity, andexanet has been shown to reverse the anti-factor IIa activity of a low molecular weight heparin, enoxaparin, *in vitro*.	In addition to reversal of ***anti-fXa***~~FXa~~ activity, andexanet has been shown to reverse the anti-factor IIa activity of a low molecular weight heparin, enoxaparin, *in vitro*.	This was an error. Updated to reflect accurate reversal activity of andexanet toward anti-fXa.	NS
1.4.3 Phase 2 Study of Andexanet with Factor Xa Inhibitors in Healthy Subjects	Administration of andexanet was associated with a rapid decrease in unbound apixaban, rivaroxaban, and edoxaban that was dose-dependent, with the greatest effect observed at the highest doses tested (420 mg dose for apixaban, and 800 mg dose for rivaroxaban and edoxaban) (Figure 2).	Administration of andexanet was associated with a rapid decrease in unbound apixaban, rivaroxaban, and edoxaban that was dose-dependent, with the greatest effect observed at the highest doses tested (420 mg dose for apixaban, and 800 mg dose for rivaroxaban and edoxaban) (Figure 2 ***and Figure 4***).	Figure reference added.	NS
3.1 Overall Study Design and Plan: Description	If the timing of the last dose of FXa inhibitor is unknown, the andexanet infusion must begin as soon as possible—following the signing of the ICF and completion of pre-treatment procedures—but no later than 3 hours following the signing of the ICF**.**	If the timing of the last dose of FXa inhibitor is unknown, the andexanet ***bolus***~~infusion~~ must begin as soon as possible—following the signing of the ICF and completion of pre-treatment procedures—but no later than 3 hours following the signing of the ICF**.**	Update to clarify that the bolus (vs colloquial use of infusion) is the administration step that must begin as soon as possible.	NS

First Section of Occurrence (& throughout document)	Old Text (from Amendment 5)	New Text (strikethrough indicates deleted text / bold italics indicates added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
3.1 Overall Study Design and Plan: Description	Adverse Events will be followed through Study Day 3 and related AEs and survival will be followed through the Day 30 post-treatment visit.	Adverse Events ***and survival*** will be followed through ~~Study Day 3 and related AEs and survival will be followed through~~ the Day 30 post-treatment visit.	Updated to include survival and simplify the description of the study periods related to safety monitoring.	NS
3.3 Duration of Study	• Safety Evaluation Period: 3 days (Days 1–3). • Extended Safety Follow-up Period (AEs, survival): ~27 days (Day 4 to the Day 30 study visit).	• Safety Evaluation Period including Follow-up Period (AEs, survival): 30 days (Day 1 to the Day 30 study visit).~~: 3 days (Days 1–3).~~ • ~~Extended Safety Follow-up Period (AEs, survival): ~27 days (Day 4 to the Day 30 study visit).~~	Updated to simplify the description of the study periods related to safety monitoring.	NS
3.4.2 Study Population	As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of FXa inhibitor within 18 hours.	As a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of FXa inhibitor within 18 hours~~.~~ ***if the timing is known. (If the timing of the last dose of FXa inhibitor is unknown, the andexanet bolus must begin as soon as possible–following signing of the ICF and completion of pre-treatment procedures–but no later than 3 hours following signing of the ICF.)***	Updated for clarity.	NS
4.2 Exclusion Criteria	1. The patient is scheduled to undergo surgery in less than 12 hours, with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes – see more examples in Appendix G).	1. The patient is scheduled to undergo surgery in less than 12 hours ***after end of andexanet infusion***, with the exception of minimally invasive surgery/procedures (e.g., endoscopy, bronchoscopy, central lines, Burr holes – see more examples in Appendix G).	Updated for clarity.	NS

First Section of Occurrence (& throughout document)	Old Text (from Amendment 5)	New Text (strikethrough indicates deleted text / bold italics indicates added text)	Rationale for Revision	Substantial (S) OR Non-substantial (NS) Change
6.2 Dosing and Administration (Table 3: Andexanet Dosing Regimens)	Edoxaban ≤ 30 mg Low Dose > 30 mg/ Unknown High Dose	Edoxaban ~~≤~~ 30 mg Low Dose ~~≥~~ 30 mg/ Unknown High Dose	Updated to reflect accurate ranges of < 30 mg (low dose) and ≥ 30 mg (high dose) for andexanet dosing in patients receiving edoxaban.	S