A RANDOMIZED CLINICAL TRIAL OF ANDEXANET ALFA IN ACUTE INTRACRANIAL HEMORRHAGE IN PATIENTS RECEIVING AN ORAL FACTOR XA INHIBITOR

DRUG NAME: Andexanet Alfa

PROTOCOL NUMBER: 18-513

PHASE: 4

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INVESTIGATOR'S AGREEMENT

I have read ALXN2070 Study18-513 Protocol Amendment 3 (dated 01 December 2022) entitled, *"A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor,"* and agree to abide by all provisions set forth therein.

I agree to conduct the study in accordance with all applicable government regulations, the principles of the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines for Good Clinical Practice (GCP), and the principles of the World Medical Association Declaration of Helsinki.

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 Alexion Pharmaceuticals, Inc.

_____
Signature of Principal Investigator

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

SPONSOR'S AGREEMENT

I have read ALXN2070 Study18-513 Protocol Amendment 3 (dated 01 December 2022) entitled *"A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor,"* and agree to abide by all provisions set forth therein.

I agree to conduct the study in accordance with all applicable government regulations, the principles of the ICH E6 Guidelines for GCP, and the principles of the World Medical Association Declaration of Helsinki.

[redacted]

[redacted]

Date (DD Month YYYY)

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Alexion Pharmaceuticals UK Ltd

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OVERVIEW OF CHANGES IN THE CURRENT AND PREVIOUS PROTOCOL AMENDMENTS

Substantial changes to the protocol in the current and previous amendments are summarized below.

Protocol Version and Date	Substantial Changes
Original Netherlands 21 March 2019	• Added Summary of Changes table to highlight document revisions • Modified Inclusion Criteria #1 to allow for 'deferred consent' procedure as allowed in emergency situations in the Netherlands. Deferred consent is consistent with the principles of emergency consent (defined as consent from a qualified medical professional) as described in Section 13.2 of the protocol. • In cases of deferred consent, the time of study physician's documented decision to include the patient into the study will serve as "time of consent" with respect to protocol-specific procedures. • In all cases where the patient does not sign informed consent form (ICF) prior to study entry, informed consent will be obtained as soon as realistically possible after inclusion in the trial and in accordance with the Declaration of Helsinki, ICH GCP, the Data Protection Directive (Directive 95/46/EC) and national and local regulations.
Original Switzerland: 13 January 2020	• Added Summary of Changes table to highlight document revisions • Added Inclusion Criteria #7 to specify required contraceptive methods • Added description of randomization code safekeeping • Added rationale for inclusion of vulnerable patients • Added reasons for discontinuation from the study • Added country specific requirements for reporting of Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI) in Switzerland • Added reporting timelines for termination, interruption and completion of the trial • Added consenting requirements for patients who were initially incapacitated but regained their decision-making capacity • Added clarification about ICH E6 R2 EDC conformity • Added information about data management of patients who refuse to participate after inclusion in the trial based on legal representative or medical proxy consent • Central laboratories specified
Protocol Amendment 1 15 April 2020	Updated eligibility criteria as follows: • Reworded Inclusion Criterion #1 for clarity and to allow for 'deferred consent' procedure. Deferred consent is consistent with the principles of emergency consent (defined as consent from a qualified medical professional) as described in Section 13.2 of the protocol. In cases of deferred consent, the time of study physician's documented decision to include the patient into the study will serve as "time of consent" with respect to protocol-specific procedures. • In all cases where the patient does not sign ICF prior to study entry, informed consent will be obtained as soon as realistically possible after inclusion in the trial and in accordance with the Declaration of Helsinki, ICH GCP, the Data Protection Directive (Directive 95/46/EC) and national and local regulations.

Protocol Version and Date	Substantial Changes
	• Updated Inclusion Criterion #2 to specify a maximum age (90 years old) for study eligibility • Modified Inclusion Criterion #3 to limit enrollment to patients with intracerebral hemorrhage to increase the homogeneity of the study population and to clarify eligible hematoma blood volume. • Reworded Inclusion Criterion #5 to exclude low dose Factor Xa (FXa) inhibitors, to clarify a scenario in which patients who received their last dose of oral FXa inhibitor >15 hours prior to randomization (or whose time since the last oral FXa inhibitor dose is unknown) may still be eligible for enrollment • Updated Inclusion Criterion #6 to decrease maximum time from bleeding symptoms onset to baseline imaging scan from 12 hours to 6 hours. • Added Inclusion Criterion #7 to provide contraception requirements, and added guidance for women of childbearing potential and men with sexual partners of childbearing potential • Added Inclusion Criterion #8 to ensure that pregnant women are not enrolled • Updated Exclusion Criterion #1 to clarify that minimally invasive surgery/procedures are allowed if they are not expected to significantly affect hematoma volume • Removed the original Exclusion Criterion #3 for intracerebral hematoma volume > 60 mL and instead included required bleed volume in Inclusion Criterion #3 (replaced Exclusion Criterion #3 with "Purposefully left blank"). • Modified Exclusion Criterion #6 for additional clarity with respect to expected survival • Added Exclusion Criterion #14 to exclude any patients with tumor-related bleeding • Added Exclusion Criterion #15 to exclude patients with a known hypersensitivity to any component of andexanet alfa (andexanet) • Added Exclusion Criterion #16 to exclude any patient with a baseline National Institutes of Health Stroke Scale (NIHSS) >35 at the time of consent • Added language to allow standard of care laboratory assessments or procedures performed at acute illness, but before signing of informed consent, to be used for assessing eligibility Updated objectives, endpoints, analyses, and study design as follows: • Added a secondary efficacy objective to evaluate the effect of andexanet versus usual care on neurologic function • Deleted the additional efficacy objective to evaluate the effect of andexanet versus usual care on clinical and functional neurologic status • Added an additional efficacy objective to evaluate the occurrence and outcome of extracranial bleeding • Added an additional efficacy objective to evaluate the effect of andexanet versus usual care on health-related quality of life • Added a safety objective to evaluate the occurrence of invasive intracranial procedures post-randomization • Updated the primary endpoint to clarify criteria required for a patient to be considered as having excellent or good hemostatic efficacy • Reworded the first secondary efficacy endpoint to percent change and added timing details

Protocol Version and Date	Substantial Changes
	• Added a secondary efficacy endpoint for the Glasgow Coma Scale (GCS) at 24 hours • Added a secondary efficacy endpoint for neurologic deterioration • Added an additional efficacy endpoint for the utility-weighted modified Rankin Scale (uw-mRS) • Updated the additional efficacy endpoint for NIHSS to include assessments at 2, 3, 6, and 72 hours • Updated the additional efficacy endpoint for GCS to include assessments at 2, 3, 6, and 72 hours • Added an additional efficacy endpoint of number of patients with a ≥ 7-point increase from baseline in NIHSS at 12 hours post-randomization • Added an additional efficacy endpoint of number of patients receiving rescue therapy between 3- and 12-hours post-randomization • Updated the additional efficacy endpoint of occurrence and outcome of non-ICH bleeding to occurrence and outcome of extracranial bleeding • Added an additional efficacy endpoint of the EuroQol-5 Dimension (EQ-5D) Questionnaire • Added a definition of bleeding mortality to the associated safety endpoint • Added a safety endpoint to assess the number of patients with invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications • Provided more detail around the re-hospitalization safety endpoint • Deleted the safety endpoint of clinically relevant changes in vital signs • Updated the analysis of the primary endpoint and removed some details that will instead be provided in the Statistical Analysis Plan (SAP) • Updated the analyses for the secondary endpoints • Updated the analyses for the additional efficacy endpoints • Added subgroup analyses based on usual care therapy received for those patients randomized to that treatment group and time since last FXa inhibitor dose, and removed subgroup analysis based on primary compartment of bleeding • Updated details on summaries to be generated to describe safety endpoints to reflect changes to safety endpoints • Updated details regarded the planned analysis of deaths • Added a section to describe the planned analysis on invasive procedures • Added details regarding the planned data to be summarized for hospitalizations • Updated alpha spending for the interim analysis • Updated definitions of efficacy analysis populations • Added section to clarify the population on which the primary and secondary endpoints will be analyzed • Updated the sample size from approximately 440 subjects to approximately 900 subjects and the number of investigational sites from approximately 100 to approximately 200 • Added stratification factors of intended-usual-care-agent and time from symptom onset to baseline imaging scan, and removed stratification by site, to the randomizations scheme

Protocol Version and Date	Substantial Changes
	• Updated the adjudication criteria for hemostatic efficacy to reflect other changes made to the protocol • Updated details on how missing data will be handled for the primary and secondary endpoints; deleted details on how missing data will be handled for the additional efficacy endpoints Corrections, clarifications, and further guidance were included as follows: • Added language to clarify that some assessments are only required at the Early Termination visit if they have not yet been performed during treatment • Added more clarity around Data Safety Monitoring Board (DSMB) roles and responsibilities • Added guidance that Investigators should consider maintaining systolic blood pressure at a target of 140 mmHg • Updated the study schematic to reflect changes to treatment and assessment timing • Updated language to require patients with a positive anti-andexanet antibody response at Day 30 to be followed after the study for up to approximately 120 days • Removed the requirement that andexanet be prepared prior to randomization for all patients • Provided guidance around the use of blood products prior to screening • Provided guidance around the use of concomitant medications, hemostatic agents, pro-coagulant treatments, surgical intervention, and rescue therapy allowed during the study • Updated language to differentiate between discontinuation of study drug and discontinuing from the study • Updated the definition of study completion • Added language to clarify timing for usual care dosing • Corrected a discrepancy that incorrectly included serious and severe infusion reactions as AESI • Clarified text around adverse event (AE) reporting • Added a section on hemostasis assessments and added NIHSS assessments at 2 hours, 24 hours, and 72 hours post-randomization • Added a section on GCS assessments, with assessments performed at baseline and at 2, 3, 6-, 12-, 24-, and 72-hours post-randomization • Clarified that procedures that might interfere with the assessment of hemostatic efficacy are to be excluded Operational changes were made as follows: • Updated roles and responsibilities of study committees • Added text to allow the Day 7 visit to be conducted by phone • Changed 15 minute time-point to 30 minute time-point relative to IP administration – dosing must be within 30 minutes from Randomization and within 120 minutes of computed tomography (CT) scan. • Increased allowable timeframe to perform the 12-hour imaging scan from 11-13 hours to 11-15 hours post-randomization.

Protocol Version and Date	Substantial Changes
	• Added language to encourage completeness in data collection and to allow for recording of Day 30 mortality status in the clinical database even if patients discontinue from the study for reasons other than withdrawal of consent • Provided clarity around the use of an independent unblinded statistician and overall blinding • Added timing details for anti-fXa activity assessments to protocol body • Added timing details for thrombin generation assessments to protocol body • Changed the window for biomarker endpoints • Updated clinical trial data, where updated data were available
Protocol Amendment 1.1 Switzerland 13 May 2020	• Added Summary of Changes table to highlight document revisions • Added description of randomization code safekeeping • Added rationale for inclusion of vulnerable patients • Added reasons for discontinuation from the study • Added country-specific requirements for reporting of SAEs and AESI in Switzerland • Added reporting timelines for termination, interruption, and completion of the trial • Added consenting requirements for patients who were initially incapacitated but regained their decision-making capacity • Added clarification about ICH E6 R2 EDC conformity • Added information about data management of patients who refuse to participate after inclusion in the trial based on legal representative or medical proxy consent • Central labs were specified
Protocol Amendment 2 29 July 2021	Updated eligibility criteria as follows: • The patient age requirement has been revised to allow those older than 90 years (Inclusion Criterion #2). • Patients with a hematoma volume of less than 0.5 mL are now excluded (Inclusion Criterion #3). • Removed “any bleeding into the epidural space” (Exclusion Criterion #4). • Clarified minimum anti-fXa activity of patients treated with direct and indirect FXa inhibitor treatment (Inclusion Criterion #5). • Enoxaparin-treated patients have been added to those eligible for study inclusion (Inclusion Criterion #5). • Clarified guidance for avoiding pregnancy (Inclusion Criterion #7). • Aligned Exclusion Criteria #10, #11, and #12 with the restricted prior medications and treatments in Section 7.1 • Removed NIHSS score > 35 at the time of consent (Exclusion Criterion #16 of Protocol Amendment 1) and added “NIHSS score ≤ 35 at the time of consent” (Inclusion Criterion #9). Updated objectives, endpoints, analyses, and study design as follows: • A table (Table 1)outlining study objectives and corresponding endpoints has been added to the protocol body (Section 2.0); aligned endpoint descriptions in Synopsis, Table 1, Section 10.5.3 and Section 10.5.4.

Protocol Version and Date	Substantial Changes
	• The secondary efficacy objective related to percent change from baseline to nadir in anti-fXa activity was changed from 3 to 2 hours post-randomization. • The secondary efficacy objective related to neurologic function has been recategorized as an additional efficacy objective. • Secondary endpoints related to neurofunctional scores (NIHSS and GCS at 24 hours) have been recategorized as additional efficacy endpoints. • Removed "occurrence and outcome of extracranial bleeding" as an additional efficacy objective and endpoint. • Added procedures to the early termination visit (Section 5.3) and clarified that the final assessment of bleeding is to be performed if the patient withdraws from the study prior to the 12-hour time point. • Antibodies to host cell protein will not be analyzed. • Added a pre-planned sample size re-estimation (SSR) (Section 10.7). Corrections, clarifications, and further guidance were included as follows: • The Introduction section has been shortened by deleting the latter subsections detailing the nonclinical and clinical experience with andexanet. In place of those subsections, the reader is referred to the Investigator's Brochure (IB), which is comprehensive and up to date. • Clarified that the baseline scan may be repeated only once (Inclusion Criterion #4). • Removed hydrocephalus from Imaging Core Laboratory assessments (Section 3.1). • Clarified criteria for discontinuation from the study (Section 4.3). • Updated reconstitution volumes and composition for andexanet (Section 6.1). • Clarified timing of andexanet administration relative to randomization (Section 3.1 and Section 6.2). • Clarified use of hemostatic agents, procoagulant blood products, and other unplanned rescue procedures and surgeries within 3 hours post randomization and adjudication by Endpoint Adjudication Committee (EAC) (Section 7.2 and Section 10.5.3.1). • Clarified requirements for reporting of abnormal laboratory findings as AEs (Section 8.1). • Added study-specific exceptions to AE and SAE reporting (Section 8.1.1). • Clarified the blinded and unblinded GCS evaluation time-points (Section 9.1.4). • Clarified scope of adjudication of primary endpoint by EAC (Section 10.5.3.1). • Updated the ANNEXA-4 study data (Section 10.3). • Minor clarifications and revisions throughout. Operational changes were made as follows: • The medical monitor has been changed. • The Sponsor identity has been updated following the acquisition of Portola by Alexion. • A section has been added on the potential risks to study participants posed by the coronavirus disease 2019 (COVID-19) pandemic (Section 3.5.1). • A definition for the end of the trial (last visit, last patient) has been added (Section 4.7).

Protocol Version and Date	Substantial Changes
	• Added temperature excursion requirements (Section 6.3). • The AE reporting (Section 8.0) has been revised to align with Alexion Global Drug Safety and data standards, and all applicable regulations and guidances. • The definition of and reporting requirements for suspected unexpected serious adverse reactions (SUSARs) have been added (Section 8.3). • The section on contraception (Section 8.9) has been revised to specify birth control methods that are considered "highly effective." Sexual abstinence has been included in this list. • The section on Investigator and administrative requirements (Section 12.0) has been revised to align with Alexion standards. • The IRB/IEC has been added to those permitted to conduct trial-related monitoring and audits (Section 12.9). • Blood pressure management has been removed from study days 7, 14, and 30 (or ET) in the Schedule of Activities (Appendix A). • An intracerebral hemorrhage-related diagnostic and therapeutic procedure was added at the Day 30/Early Termination visit (Appendix A). • The sepsis definition was updated (Appendix I).
Protocol Amendment 2.1 United States 02 September 2021	Revised Inclusion Criterion #1 (Synopsis and Section 4.1) Section 12.2 (Informed Consent), and the Schedule of Activities (Appendix A) to remove deferred consent as an option for study entry.
Protocol Amendment 2.2 Switzerland 18 November 2021	All changes described above for Protocol Amendment 2 dated 29 July 2021 were incorporated into this amendment. The Switzerland-specific changes implemented in Protocol Amendment 1.1 Switzerland, dated 13 May 2020, have been maintained.
Protocol Amendment 2.3 Russia 31 January 2022	Added Appendix M for clinical trial sites in Russia (Enrollment of Patients Who Cannot Provide Their Own Consent); and added references to Appendix M to the protocol synopsis (Inclusion Criterion #1), Section 3.1 (Overall Study Design and Plan), Section 3.3 (Duration of Study), Section 4.1 (Inclusion Criterion #1), Section 5.1.1 (Screening and Enrollment), Section 12.2 (Informed Consent), Section 14.0 (List of Appendices), and Appendix A (Schedule of Activities).
Protocol Amendment 3 dd Month 2022	• Updated efficacy objectives and endpoints to include timepoints that were omitted in error in the Synopsis, Table 1, and Section 10.5.3.3. • Clarified interim analysis stopping criteria based on primary efficacy endpoint. • Deleted "or > 0.5 IU/mL for enoxaparin" from "If a local anti-fXa activity level… high andexanet dosing regimen" in the Synopsis, Section 3.1, Section 3.3, Section 4.1, Table 4. • Clarified in Synopsis that an interim analysis will be done when 450 patients complete their treatment period, and DSMB is to recommend early stopping process with relevant criteria. • Removed stratification factor of intended-usual-care-agent from analyses from the Synopsis, Section 10.5.4.4, and Section 10.6.3. • Clarified that local laboratory assays should be performed at specific timepoints as per Schedule of Activities. However, the requirements to perform complete assay panels described in Section 9.2.2. is only if available as per study site standard of care. • Updated that All ITT patients will be included in the primary analysis. Patients with non-evaluable hemostatic efficacy due to clinical reasons will be treated as treatment failures in Section 10.5.3.1.

Protocol Version and Date	Substantial Changes
	• Updated text for primary efficacy endpoint analysis to include “excellent or good as adjudicated by the blinded EAC”, “difference in proportions, and the proportions from the two groups”, and “analysis, OR p<” in Section 10.5.4.2.

PROTOCOL SYNOPSIS

Title	**A Randomized Clinical Trial of Andexanet Alfa in Acute Intracranial Hemorrhage in Patients Receiving an Oral Factor Xa Inhibitor**
Study Number	18-513
Study Phase	4
Total Number of Centers	Approximately 250 sites in North America, Europe, and Asia
Objectives	In oral Factor Xa (FXa) inhibitor-treated patients with acute intracerebral bleeding, the objectives of this study are as follows: **Primary Efficacy Objective:** • To evaluate the effect of andexanet alfa (andexanet) versus usual care on the rate of effective hemostasis. **Secondary Efficacy Objective:** • To evaluate the effect of andexanet versus usual care on anti-fXa activity. **Additional Efficacy Objectives:** • To evaluate the effect of andexanet versus usual care on thrombin generation. • To evaluate the effect of andexanet versus usual care on neurologic function. • To assess the relationship between anti-fXa activity and the achievement of hemostatic efficacy. • To evaluate the effect of andexanet versus usual care on health-related quality of life. **Safety Objectives:** • To evaluate the occurrence of thrombotic events (TEs) at 30 days after randomization. • To evaluate in-hospital and 30-day mortality (all-cause, cardiovascular [CV], and bleeding). • To evaluate the occurrence of invasive intracranial procedures post-randomization. • To evaluate the length of initial hospitalization for primary bleeding event. • To evaluate the rate of re-hospitalization at 30 days after randomization. • To evaluate adverse events (AEs) and vital signs. • To evaluate the immunogenicity of andexanet.
Study Design	This is a randomized, multicenter clinical trial designed to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracerebral hemorrhage within 6 hours of symptom onset (from the baseline scan) and within 15 hours of taking an oral FXa inhibitor (from randomization). The study will use a prospective, randomized, open-label design, as it is unfeasible to blind the Investigator to the treatment assignment given the many potential therapeutic options available under usual care treatment. The primary efficacy outcome will be adjudicated by a blinded Endpoint Adjudication Committee (EAC). To support the adjudication of hemostatic efficacy, a blinded Imaging Core Laboratory will review all available scans. Approximately 900 patients are planned to be enrolled in the study. Once the Informed Consent Form (ICF) is signed, eligibility criteria are confirmed, and baseline assessments are performed, patients will be randomized 1:1 to receive either andexanet or usual care stratified by the site's intended-usual-care-agent response and also the time from symptom onset to baseline scan. Randomization must occur within 15 hours

	following the last dose of the FXa inhibitor. If a standard of care local anti-fXa activity level obtained within 2 hours prior to consent is > 100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban or edoxaban), the patient may be enrolled, irrespective of the time of the last dose, and the patient should receive the high andexanet dosing regimen. These measures are designed to ensure patients have sufficiently high anti-fXa activity. Usual care will consist of any treatment(s) (including no treatment) other than andexanet administered within 3 hours post-randomization that the Investigator and/or other treating physicians consider to be appropriate. For andexanet treatment, patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received and the amount and timing of the most recent dose. Andexanet will be given via an intravenous (IV) bolus administered over ~15 minutes (low dose) to 30 minutes (high dose) followed immediately by a continuous infusion administered over ~120 minutes. There will be no cross-over between treatment groups. It is intended that all patients initiate treatment as soon as possible after the treatment allocation is known. For: 1) anti-fXa activity; and 2) diagnostic evaluations to support hemostatic efficacy (i.e., imaging tests, National Institutes of Health Stroke Scale [NIHSS]), baseline is defined as the most recent assessment within 15 minutes and 120 minutes prior to randomization, respectively. For post-baseline efficacy assessments, time 0 is defined as randomization. AEs including serious AEs (SAEs) and TEs, and survival will be followed through the Day 30 post-treatment visit for all patients (or to day 120 if applicable). The study Schedule of Activities can be found in Appendix A. The primary efficacy endpoint will be adjudicated based on data collected through 12 hours post-randomization. The following data are planned to be captured: imaging and clinical elements (brain Magnetic Resonance Imaging [MRI] or Computed Tomography [CT]), assessment using the National Institutes of Health Stroke Scale (NIHSS) performed by a person blinded to treatment allocation (Appendix E), and concomitant medication entry and hospital records for rescue therapy. The blinded, independent EAC will oversee the adjudication of hemostatic efficacy, as well as all deaths and potential TEs. All source documents will be redacted to maintain the blinding of the EAC. The independent EAC will be blinded to all anti-fXa activities and treatment assignments. An independent Data Safety Monitoring Board (DSMB) will periodically review all safety data in aggregate, and also conduct one formal interim analysis on the primary efficacy endpoint after approximately 50% (450 patients) of the anticipated sample size has been adjudicated. The DSMB will be empowered to make recommendations regarding study modification or to suggest stopping the study early for reasons related to balance of risk and benefit. The DSMB Charter outlines all activities of this Committee. If the decision is not to stop, a pre-planned sample size re-estimation (SSR) will be performed by the blinded DSMB statistician to reassess the required size of the study population based on estimation of the primary endpoint at the interim analysis. The maximum total number of patients enrolled may be increased to 1200 patients (with the maximal 300 additional patients). The SSR will be based on a conditional power (CP) using a promising zone with the boundary of 30% to 90%.
Study Periods	The study duration for most patients will be up to 37 days. The study duration includes 3 study periods as follows: • Screening and Baseline Period: < 1 day (Day 1) • Treatment Period: < 1 day (Day 1) • Follow-up Period (all AEs, survival, antibodies): ~30 days (Day 1 to the Day 30 study visit)

	Patients with a positive anti-andexanet antibody response at the Day 30 visit should have additional follow up to approximately 120 days post-randomization.
Inclusion Criteria	All of the following criteria must be met for the patient to be eligible: 1. Written informed consent. Either the patient or his or her legally authorized representative (LAR) if permissible by local or regional laws and regulations has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening. o Deferred consent procedure is allowed where approved by local ethics committees. In cases of deferred consent, the time of the study physician's documented decision to include the patient into the study will serve as "time of consent" with respect to protocol-specific procedures. o In all cases where the patient does not sign informed consent prior to study entry, informed consent from the patient (or LAR) will be obtained as soon as realistically possible after inclusion in Study 18-513 and in accordance with the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the EU General Data Protection Regulation (GDPR), and national and local regulations. 2. Age ≥ 18 years old at the time of consent. 3. An acute intracerebral bleeding episode, defined as an estimated blood volume of ≥ 0.5 mL to ≤ 60 mL acutely observed radiographically within the cerebrum. Patients may have extracerebral (e.g., subdural, subarachnoid, epidural) or extracranial (e.g., gastrointestinal, intraspinal) bleeding additionally, but the intracerebral hemorrhage must be considered the most clinically significant bleed at the time of enrollment. 4. Performance of a head CT or MRI scan demonstrating the intracerebral bleeding within 2 hours prior to randomization (the baseline scan may be repeated only once to meet this criterion). 5. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], or edoxaban [last dose 30 mg or greater]: o ≤ 15 hours prior to randomization. o > 15 hours prior to randomization or unknown time of last dose, only if 1) the local anti-fXa activity > 100 ng/mL for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban), and 2) the local anti-fXa activity level is obtained within 2 hours prior to consent, performed as per standard of care. Note: Patients enrolled in this manner should receive a high andexanet dosing regimen. 6. Time from bleeding symptom onset ≤ 6 hours prior to the baseline imaging scan. Time of trauma (if applicable) or time last seen normal may be used as surrogates for time of symptom onset. (If the baseline scan is repeated to meet Inclusion Criterion #4, the time from bleeding symptom onset must be ≤ 6 hours prior to the repeat baseline imaging scan.) 7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy for 30 days after the last dose of study drug. 8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential). 9. NIHSS score ≤ 35 at the time of consent.

Exclusion Criteria	If a patient meets any of the following criteria, he/she is not eligible to participate in this trial. 1. Planned surgery, including Burr holes for hematoma drainage, within 12 hours after randomization. Minimally invasive surgery/procedures not directly related to the treatment of intracranial bleeding and that are not expected to significantly affect hematoma volume are allowed (e.g., Burr holes for intracranial pressure monitoring, endoscopy, bronchoscopy, central lines—Section 7.2, Section 7.3 and Appendix G). 2. Glasgow Coma Scale (GCS) score < 7 at the time of consent. If a patient is intubated and/or sedated at the time of consent, they may be enrolled if it can be documented that they were intubated/sedated for non-neurologic reasons within 2 hours prior to consent. 3. *Purposefully left blank to align with the programmed database.* 4. Anticipation that the baseline and follow up brain scans will not be able to use the same imaging modalities (i.e., patients with a baseline CT scan should have a CT scan in follow up; similarly, for MRI). 5. Expected survival of less than 1 month (not related to the intracranial bleed). 6. Recent history (within 2 weeks) of a diagnosed TE or clinically relevant symptoms of the following: o Venous Thromboembolism (VTE: e.g., deep venous thrombosis, pulmonary embolism [PE], cerebral venous thrombosis), myocardial infarction (MI), Disseminated Intravascular Coagulation (DIC), cerebral vascular accident, transient ischemic attack (TIA), acute coronary syndrome, or arterial systemic embolism (see Appendix H for DIC scoring algorithm). 7. Acute decompensated heart failure or cardiogenic shock at the time of randomization (see Appendix I for cardiogenic shock definition). 8. Severe sepsis or septic shock at the time of randomization (see Appendix I for sepsis definition). 9. The patient is a pregnant or lactating female. 10. Receipt of any of the following drugs or blood products within 7 days prior to consent: 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®), or anti-inhibitor coagulant complex (e.g., FEIBA®), FFP, and whole blood. 11. Past use of andexanet (or planned use of commercial andexanet). 12. Treatment with an investigational drug < 30 days prior to consent. 13. Any tumor-related bleeding. 14. Known hypersensitivity to any component of andexanet.

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:

Dose	Initial IV Bolus	Follow-on IV Infusion
Low	400 mg at a target rate of 30 mg/min for ~15 minutes	480 mg at a target rate of 4 mg/min for 120 minutes
High	800 mg at a target rate of 30 mg/min for up to ~30 minutes	960 mg at a target rate of 8 mg/min for 120 minutes

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	≥ 8 Hours	> 15 Hours or Unknown[a]
Rivaroxaban	10 mg	Low Dose	Low Dose	High Dose
	> 10 mg	High Dose		
Apixaban	≤ 5 mg	Low Dose		
	> 5 mg	High Dose		
Edoxaban	30 mg	Low Dose		
	> 30 mg	High Dose		

[a] ONLY if 1) the local anti-fXa activity > 100 ng/mL for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban), and 2) the standard of care local anti-fXa activity level is obtained within 2 hours prior to consent.

Endpoints	**Primary Efficacy Endpoint** Effective hemostasis 12 hours post-randomization as determined by the blinded EAC. **Secondary Efficacy Endpoint** • Percent change from baseline to nadir in anti-fXa activity during the first 2 hours post-randomization. **Additional Efficacy Endpoints** • Change from baseline in thrombin generation parameters (with Endogenous Thrombin Potential [ETP] as the primary measure) obtained at 1 and 12 hours post-randomization. • Proportion of neurologic deterioration, as defined by an NIHSS score increase ≥ 4 or a GCS score decrease ≥ 2 at 24 hours post-randomization versus baseline. • Change from baseline in Modified Rankin Scale (mRS) score at 30 days post-randomization. • Change from baseline in NIHSS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization • Change from baseline GCS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization. • Proportion of patients with a ≥ 7-point increase from baseline in NIHSS score at 12 hours post-randomization. • Hemostatic efficacy evaluated using only imaging parameters. • Proportion of patients receiving rescue therapy between 3 and 12 hours post-randomization. • Correlation analysis between anti-fXa activity and the achievement of hemostatic efficacy. • Health-related quality of life as assessed by the EuroQol-5 Dimension (EQ-5D) questionnaire at 30 days post-randomization. • Utility-weighted Modified Rankin Scale (uw-mRS) score at 30 days post-randomization. **Safety Endpoints** • Occurrence of TEs, confirmed by adjudication, through 30 days post-randomization. • In-hospital mortality (during index hospitalization; all-cause, CV, and bleeding). • 30-day all-cause, CV, and bleeding related mortality (defined as any death within 72 hours from randomization and not associated to the occurrent of an identified TE event). • Proportion of patients with invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications. • Length of initial hospitalization for primary bleeding event. • Total time admitted to the intensive care unit during the initial hospitalization. • Proportion of re-hospitalizations, including total number of re-hospitalizations and total days re-hospitalized, at 30 days post-randomization. • AEs and vital signs. • Antibodies to Factor X (FX), FXa, and andexanet. • Neutralizing antibodies to FX, FXa, and andexanet.

Sample Size and Statistical Power	Approximately 900 patients (i.e., 450 patients per group) will be randomized 1:1 to receive either andexanet or usual care. After accounting for early discontinuation rate and the type I error associated with the interim analysis, this sample size should have approximately 90% power to detect a 10% absolute difference between andexanet and usual care in the rate of effective hemostasis at an overall 0.05 two-sided overall significance level. The rate of effective hemostasis is estimated to be approximately 70% and 80% for usual care and andexanet, respectively. The expected rate of effective hemostasis in the andexanet population is based on efficacy results from ANNEXA-4. A 10% higher rate of effective hemostasis represents a 33% risk reduction of not achieving it from the usual care, which is considered clinically meaningful.
Statistical Analysis	The primary objective of the study is to compare the proportion of patients with effective hemostasis (excellent or good as adjudicated by the blinded EAC) between andexanet and usual care). For a patient to have excellent or good hemostatic efficacy, he or she must meet all of the following criteria: • NIHSS score of less than +7 point change from the baseline score at 12 hours post-randomization • No greater than 35% increase from baseline in hematoma volume at 12 hours post-randomization • Have not received rescue therapy (as defined in Section 7.4) between 3 and 12 hours post-randomization The following hypothesis will be evaluated: H_0: $\pi_{UC} - \pi_{andexanet} = 0$ H_A: $\pi_{UC} - \pi_{andexanet} \neq 0$ Analysis will be performed using a Cochran-Mantel Haenszel (CMH) test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes). The corresponding 95% confidence intervals for the difference in the proportion of participants with effective hemostasis between andexanet and usual care, and for the proportions will be provided. Missing values and/or non-evaluable hemostatic efficacy will be imputed. The study will be considered to have met its primary efficacy objective if (1) the proportion of andexanet-treated patients with effective hemostasis is significantly higher than that in patients randomized to usual care with $p < 0.0310$ at interim analysis when approximately 50% (450 patients) of the anticipated sample size has been adjudicated for their hemostatic data; or (2) $p < 0.0277$ at the end of the study. If the primary endpoint is statistically significant, the secondary endpoint will be tested at the same alpha level. The secondary endpoint is the percent change in anti-fXa activity from baseline to nadir during the first 2 hours post-randomization. The analysis of this endpoint will be an Analysis of Covariance (ANCOVA) on the ranked data, including time from symptom onset to baseline imaging scan (< 180 minutes vs. ≥ 180 minutes), and baseline anti-fXa activity as covariates. The final analysis is controlled in a similar fashion using an alpha level of 0.0277. The overall family-wise error rate is controlled at alpha level of 0.05 and accounts for the interim and final analyses for the primary and secondary endpoints. Neurological status at 24 hours compared with baseline according to scoring on the NIHSS and GCS is included among the additional efficacy endpoints. The change from baseline to hour 24 for each scale will be analyzed using a linear mixed effects model while the binary

	variable (proportion of neurological deterioration at 24 hours) will be analyzed using a stratified CMH test. The individual thrombin generation and mRS score (ordinal, dichotomous, and utility-weighted analyses) will be analyzed as well. For additional efficacy analysis refer to the Statistical Analysis Plan.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	AEs of Special Interest
ANCOVA	Analysis of Covariance
Andexanet	Andexanet Alfa
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel Haenszel
COVID	Coronavirus Disease 2019
CP	Conditional Power
CRF	Case Report Form
CT	Computed Tomography
cTn	cardiac Troponin
CV	Cardiovascular
DBP	Diastolic Blood Pressure
DIC	Disseminated Intravascular Coagulation
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
EAC	Endpoint Adjudication Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ED	Emergency Department
EDC	Electronic Data Capture
EQ-5D	EuroQol-5 Dimension
ETP	Endogenous Thrombin Potential
FDA	(US) Food and Drug Administration
FFP	Fresh Frozen Plasma
FX	Factor X
FXa	Factor Xa
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Definition
ICrH	Intracranial Hemorrhage
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
LAR	Legally Authorized Representative
LBBB	left bundle branch block
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PaO_2/FIO_2	Arterial oxygen partial pressure/fractional inspired oxygen
PCC	Prothrombin Complex Concentrate
PD	Pharmacodynamic
PE	Pulmonary Embolism
PK	Pharmacokinetic
PP	Per Protocol
PRBC	Packed Red Blood Cell
rfVIIa	Recombinant factor VIIa
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SSR	Sample Size Re-estimation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TE	Thrombotic Event
TEAE	Treatment-Emergent Adverse Event
TFPI	Tissue Factor Pathway Inhibitor
TIA	Transient Ischemic Attack
ULN	Upper Limit of Normal
US	United States
uw-mRS	Utility-weighted modified Rankin Scale
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism
WBC	White blood cells
WHO-DD	World Health Organization Drug Dictionary

1.0 INTRODUCTION

The class of Novel Oral Anticoagulants known as direct Factor Xa (FXa) inhibitors has consistently demonstrated comparable or superior efficacy and/or safety relative to its predecessors, Vitamin K Antagonists (VKAs) and Low Molecular Weight Heparins. These agents (apixaban [Eliquis®], betrixaban [BevyxXa®], edoxaban [Savaysa®], rivaroxaban [Xarelto®]) are approved for the prevention of serious thromboembolic outcomes (e.g., stroke, deep vein thrombosis [DVT], pulmonary embolism [PE]) and have become widely used in the United States (US) and worldwide. One limitation to the use of FXa inhibitors has been the lack of an antidote to be used in cases of severe and/or life-threatening bleeding events. Acute major bleeding occurs at observed rates of 2-4% in pivotal stroke prevention trials in patients with nonvalvular atrial fibrillation [1-3], and such events are often catastrophic. Given the wide adoption and increasing use of FXa inhibitors, the prospect of major bleeding, especially in Intracranial Hemorrhage (ICrH) patients, has become a significant unmet medical need.

Among the various types of bleeding, the most serious and consequential is ICrH, including intracerebral/intraventricular, subdural, subarachnoid, and epidural bleeding. Patients with ICrH have particularly dismal outcomes, with 30-day mortality rates in excess of 30-40% [1-3] and a 75% 1-year incidence of severe disability or death [4]. In the management of patients with ICrH, a primary therapeutic goal is the prevention of hematoma expansion, which has been strongly associated with morbidity and mortality [5]. While investigation of the impact of hematoma expansion is limited by a lack of a unifying definition [6], a general consensus has arisen in recent years that a relative volume increase of 30-35% or less compared to baseline is indicative of a lack of expansion [7-9].

For anticoagulated patients presenting with major bleeding, one key treatment objective is to rapidly reverse the effects of anticoagulation. It is known from experience with VKA-related bleeding that reversal of anticoagulation is associated with improved hemostatic efficacy [7] and reduced mortality [10]. In bleeding patients anticoagulated with the direct thrombin inhibitor dabigatran, treatment with idarucizumab, a monoclonal antibody against dabigatran, results in a rapid and durable reversal of dilute thrombin time and ecarin clotting time [11]. However, until recently no agents had been approved for reversing the anticoagulation related to oral FXa inhibitors. In addition, it is not known if reversal of anticoagulation is beneficial specifically to patients with ICrH.

Andexanet alfa (andexanet), a rationally designed, recombinant analog of endogenous human FXa, has been developed to rapidly and potently reverse FXa inhibition and restore physiologic coagulation. It was granted accelerated approval by the US Food and Drug Administration (FDA) in 2018 and initial conditional marketing authorization by the European Commission in 2019. Clinical studies to date have shown that andexanet rapidly reverses FXa inhibition in healthy volunteers and in bleeding patients, including those with ICrH. Andexanet is also associated with a high rate of clinical hemostasis in patients with ICrH and in patients with other

types of major bleeding. Details of the nonclinical and clinical experience with andexanet, including guidance for the Investigator, can be found in the Investigator's Brochure (IB).

Andexanet has not been compared to usual care in a randomized trial. The present randomized trial will be performed to demonstrate improved hemostatic efficacy with andexanet compared to usual care in patients with acute intracerebral hemorrhage while taking an oral FXa inhibitor.

2.0 STUDY OBJECTIVES

Table 1 summarizes the objectives and endpoints of this study in oral FXa inhibitor-treated patients with acute intracerebral hemorrhage.

Table 1: Study 18-513: Objectives and Endpoints

Objectives	Endpoints
PRIMARY EFFICACY	
• Evaluate the effect of andexanet versus usual care on the rate of effective hemostasis.	• Effective hemostasis 12 hours post-randomization as determined by the blinded EAC.
SECONDARY EFFICACY	
• Evaluate the effect of andexanet versus usual care on anti-fXa activity.	• Percent change from baseline to nadir in anti-fXa activity during the first 2 hours post-randomization.
ADDITIONAL EFFICACY	
• Evaluate the effect of andexanet versus usual care on thrombin generation.	• Change from baseline in thrombin generation parameters (with ETP as the primary measure), obtained at 1 and 12 hours post-randomization.
• Evaluate the effect of andexanet versus usual care on neurologic function.	• Proportion of neurologic deterioration, as defined by an NIHSS score increase ≥ 4 or a GCS score decrease ≥ 2 at 24 hours post-randomization versus baseline.
	• Change from baseline in mRS score at 30 days post-randomization.
	• Change from baseline in NIHSS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization.
	• Change from baseline GCS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization.
	• Proportion of patients with a ≥ 7-point increase from baseline in NIHSS score at 12 hours post-randomization.
	• Hemostatic efficacy evaluated using only imaging parameters.
	• Proportion of patients using rescue therapy between 3 and 12 hours post-randomization.
• Assess the relationship between anti-fXa activity and the achievement of hemostatic efficacy.	• Correlation analysis between anti-fXa activity and the achievement of hemostatic efficacy.
• Evaluate the effect of andexanet versus usual care on health-related quality of life.	• Health-related quality of life as assessed by the EQ-5D questionnaire at 30 days post-randomization.
	• UW-mRS score at 30 days post-randomization.

Table 1: Study 18-513: Objectives and Endpoints

Objectives	Endpoints
SAFETY	
● Evaluate the occurrence of TEs at 30 days after randomization.	● Occurrence of TEs, confirmed by adjudication, through 30 days post-randomization.
● Evaluate in-hospital and 30-day mortality (all-cause, CV, and bleeding).	● In-hospital mortality (during index hospitalization; all-cause, CV, and bleeding).
	● 30-day all-cause, CV, and bleeding related mortality (defined as any death within 72 hours from randomization and not associated to the occurrence of an identified TE event).
● Evaluate the occurrence of invasive intracranial procedures post-randomization.	● Proportion of patients with invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications.
● Evaluate the length of initial hospitalization for primary bleeding event.	● Length of initial hospitalization for primary bleeding event.
	● Total time admitted to the intensive care unit during the initial hospitalization.
● Evaluate the rate of re-hospitalization at 30 days after randomization.	● Proportion of re-hospitalizations, including total number of re-hospitalizations and total days re-hospitalized, at 30 days post-randomization.
● Evaluate AEs and vital signs.	● AEs and vital signs.
● Evaluate the immunogenicity of andexanet.	● Antibodies to FX, FXa, and andexanet.
	● Neutralizing antibodies to FX, FXa, and andexanet.

AE = adverse event; CV = cardiovascular; EQ-5D = EuroQol-5 Dimension; ETP = endogenous thrombin potential; FX = Factor X; FXa = Factor Xa; GCS = Glasgow Coma Scale; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TE = thrombotic event; uw-mRS = utility-weighted modified Rankin Scale.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan: Description

This is a randomized clinical trial to determine the efficacy and safety of andexanet compared to usual care in patients presenting with acute intracerebral hemorrhage within 6 hours of symptom onset (from the baseline scan) and within 15 hours of taking an oral FXa inhibitor (from randomization). The study will use a prospective, randomized, open-label design, as it is unfeasible to blind the Investigator to the treatment assignment given the many potential therapeutic options available under usual care treatment. The primary efficacy outcome will be adjudicated by a blinded Endpoint Adjudication Committee (EAC).

Patients will typically be enrolled in the Emergency Department (ED) upon presentation with an acute intracerebral bleeding episode. However, patients who experience an acute intracerebral hemorrhage while hospitalized in other hospital departments may also be enrolled. Approximately 900 patients will be enrolled in the study at approximately 250 sites in North America, Europe, and Asia.

Once the Informed Consent Form (ICF) is signed, eligibility criteria are confirmed, baseline assessments are performed, and the site's intended-usual-care-agent answer (see Section 3.2.1) is documented, patients will be randomized 1:1 to receive either andexanet or usual care, stratified by the site's intended-usual-care-agent response and also the time from symptom onset to baseline scan. Randomization must occur within 15 hours following the last dose of FXa inhibitor. If a local anti-fXa activity obtained within 2 hours prior to consent is > 100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban or edoxaban), and performed as per standard of care, the patient may be enrolled if the time of last FXa inhibitor dose is >15 hours or the time of the last dose is unknown, and the patient should receive the high andexanet dosing regimen. These measures are designed to ensure patients have sufficiently high anti-fXa activity. Specific instructions related to anti-fXa activities obtained at a local laboratory are contained in the Laboratory Manual.

Usual care will consist of any treatment(s) (including no treatment) other than andexanet initiated within 3 hours post-randomization that the Investigator and/or other treating physicians consider to be appropriate. For andexanet treatment, patients will receive one of two dosing regimens of andexanet based on which FXa inhibitor they received (see Section 6.2) and the amount and timing of the most recent dose.

Andexanet dosing should be initiated no later than 30 minutes after randomization and preferably within 2 hours of the baseline brain imaging scan (Figure 1). To accommodate dosing within 2 hours of the baseline scan closest to randomization, reconstitution of andexanet prior to randomization will be allowed. Andexanet will be given as an intravenous (IV) bolus administered over ~15 minutes (low dose) to 30 minutes (high dose), followed immediately by continuous infusion administered over ~120 minutes. There will be no cross-over between

treatment groups. Patients may be treated for bleeding with any unplanned rescue medications or intervention deemed to be clinically warranted, except andexanet in the usual care arm (see Section 7.2, Section 7.3, and Section 7.4 for specific guidance on use of rescue and concomitant medications).

It is intended that all patients initiate treatment as soon as possible after randomization. Patients allocated to andexanet arm should commence andexanet no later than 30 minutes post-randomization and preferably within 2 hours of the baseline brain imaging scan. A schematic for events of a patient's involvement in the study from baseline through approximately 12 hours after randomization can be found in Figure 1.

Figure 1: Events Through the First 12 Hours After Enrollment

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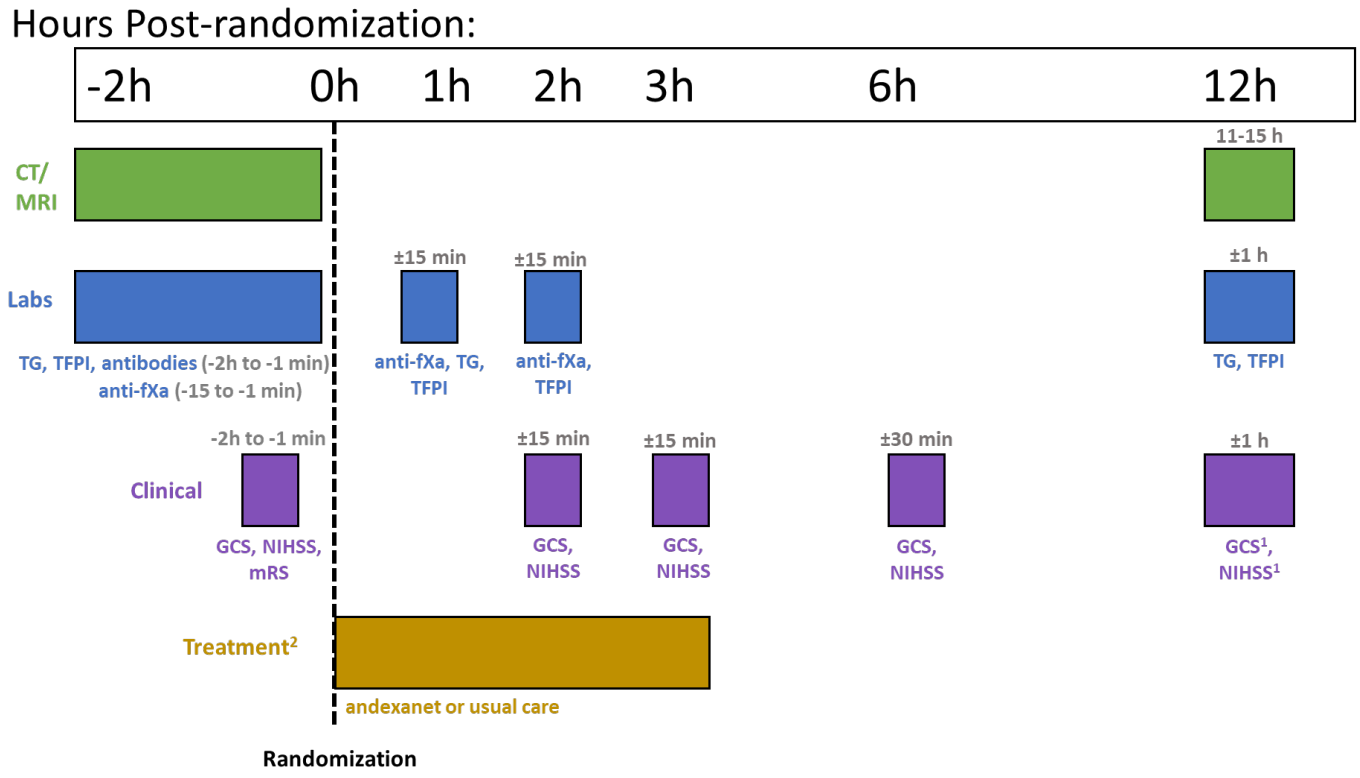

1 Blinded evaluation at 12 hours and 24 hours post-randomization

2 Reconstitution of andexanet prior to randomization will be allowed. Initiation of dosing should occur no later than 30 minutes after randomization and preferably within 2 hours of the baseline head scan.

CT = computed tomography; FXa = Activated Factor Xa; GCS = Glasgow Coma Scale; h = hour; labs = laboratories; min = minutes, MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NIHSS = National Institutes of Health Stroke Scale; TFPI=Tissue Factor Pathway Inhibitor; TG = thrombin generation

Note: Dosing procedures begin after randomization. Andexanet will be given as a bolus over 15-30 minutes followed by 120-minute continuous infusion. Treatment duration of usual care is dependent upon available therapy. A detailed listing of study procedures, including additional laboratory samples Day 1 through Day 30 is detailed in Appendix A.

Following baseline assessments, imaging evaluation will be performed at approximately 12 hours following randomization. All scans for individual patients should utilize a consistent imaging modality, scanner, and acquisition protocols/techniques whenever possible. Primary neurologic assessment will consist of evaluation of the National Institutes of Health Stroke Scale (NIHSS) at baseline and at 12 hours. The 12-hour and 24-hour assessments will be performed by study personnel who are blinded to the treatment allocation of the patient. Additional NIHSS measurements performed at 2 hours, 3 hours, 6 hours, and 72 hours will be performed for safety monitoring purposes; these measurements may be blinded or unblinded. Following the 12-hour assessment, patients will return for a follow-up visit at Day 30 (+7) and follow-up phone calls on Day 7 (+3) and Day 14 (+6). s (a detailed Schedule of Activities is provided in Appendix A). An additional visit is required for patients with a positive anti-andexanet antibody response at the Day 30 visit approximately 120 days post-randomization, or within 30 days of when the positive test is made known to the Investigator, whichever is later.

The adjudication of hemostatic efficacy will be overseen by an independent EAC, using a rating system developed based on the study from Sarode, et al [7] (Appendix B) and updated in recent International Society on Thrombosis and Haemostasis guidelines on hemostasis endpoints in clinical trials [9]. For this study, hemostatic efficacy will be based on assessment of neurologic status determined by NIHSS, and the use of rescue therapy, in addition to hematoma expansion. Hematoma expansion between baseline and 12 hours will be assessed using serial brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) read by a blinded core laboratory, and clinical assessment will be done by study personnel blinded to treatment allocation. Effective hemostasis (i.e., a rating of "good" or "excellent") will be defined as no greater than a 35% increase in hematoma volume AND no neurologic deterioration on the NIHSS of +7 or greater at 12 hours post-randomization, AND no administration of rescue therapy between 3 hours and 12 hours post-randomization (defined in Section 7.4). A patient that meets any of these 3 criteria will be considered to have "symptomatic hematoma expansion."

The EAC will also adjudicate all potential TEs (AEs of special interest [AESI]) and deaths. The EAC will be blinded to all anti-fXa activity levels and treatment assignment. Detailed practices and policies of the EAC will be delineated in a separate Adjudication Charter.

The Imaging Core Laboratory readers will be blinded to treatment assignment, anti-fXa activity adjudicated outcomes, and clinical management for all patients, and, to the extent possible, will use the same standardized methodology to analyze all scans. Parameters to be measured include, but are not limited to location of hematoma, hematoma volume and midline shift. The policies and procedures of the Imaging Core Laboratory will be detailed in separate guidance documents, which include a Core Laboratory Charter and/or Standard Operating Procedures.

To provide oversight of safety monitoring and to review the interim efficacy and safety data while the study is ongoing, a Data Safety Monitoring Board (DSMB) will be convened (see Section 10.7). The DSMB will meet periodically, approximately every 6 months to review efficacy and safety data. A formal interim analysis of efficacy will be conducted after approximately 50% of the anticipated sample size has been adjudicated. Safety outcomes to be evaluated include Serious Adverse Events (SAEs) and other AEs, with special attention to TEs (AESI). The DSMB will determine whether the occurrence of TEs in aggregate (related or not) warrant changes to the study. The DSMB may recommend termination of the study for efficacy results beyond reasonable doubt, or for any safety concern that is felt to outweigh potential benefits, wherein clear, consistent, and persistent evidence of net harm that overwhelms any benefit should be apparent. The DSMB rules to modify the study design or stop the study for safety or efficacy will be detailed in the DSMB Charter.

To minimize the effects of blood pressure on hematoma expansion, Investigators are reminded to have a goal of maintaining systolic blood pressure (SBP) at a target of 140 mm Hg as medically warranted in both treatment arms [12]. Use and timing of administration of Packed Red Blood Cell (PRBC) transfusion, transfusion of other blood products (e.g., whole blood, platelets, plasma), administration of coagulation factors and hemostatic agents, and diagnostic or therapeutic procedures for bleeding following randomization will be documented in the Case Report Forms (CRFs).

3.2. Blinding and Randomization

3.2.1. Randomization

This study will be randomized 1:1 andexanet to usual care, stratified by:

- Intended-usual-care-agent; and
- Time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes).

To account for potential differences in the demographics or baseline severity of patients who receive Prothrombin Complex Concentrate (PCC) products (e.g., KCentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®), anti-inhibitor coagulant complex (e.g., FEIBA®), or other plasma-derived coagulation factor concentrates, or a regional difference in the use of these agents, randomization will be stratified by an intended-usual-care-agent (plasma-derived coagulation factor concentrates vs. other) determined on a patient-by-patient basis. The intended-usual-care-agent is determined by the Investigator and is the Investigator's best determination of what type of therapy will be used for the patient, in the event that the patient is randomized to the usual care arm. In addition, to account for potential imbalances between treatment groups in baseline factors known to be predictive of hematoma expansion, randomization will also be stratified by the time from symptom onset to baseline imaging scan (< 180 minutes vs ≥ 180 minutes). The randomization scheme will be generated by the Sponsor.

3.2.2. Blinding

To avoid bias, the study treatment assignment and anti-fXa activity levels will be blinded to the independent EAC and the Imaging Core Laboratory. However, because of the many therapeutic options available to Investigators to treat patients randomized to usual care, it is considered unfeasible to blind all study personnel (especially those directly involved in the care of an enrolled patient) to treatment assignment. Thus, the study treatment allocation of each patient will be unblinded to the local Investigator and most of the local site study team. However, to perform neurologic assessments to support efficacy endpoints (particularly NIHSS and Glasgow Coma Scale [GCS]) at 12- and 24-hours following randomization, individuals at each site who are tasked with these assessments at these time-points will be blinded. Furthermore, the Sponsor will remain blinded to adjudication outcomes, post-randomization anti-fXa activities, and imaging results. Blinding processes and procedures are outlined in a separate Blinding Plan.

3.3. Duration of Study

The study duration for most patients will be up to 37 days. Data collection and follow up begins once informed consent is signed. The study duration includes 3 study periods as follows:

- Screening and Baseline Period: < 1 day (Day 1)
- Treatment Period: < 1 day (Day 1)
- Follow-Up Period (all AEs, survival, antibodies): ~30 days (Day 1 to the Day 30 study visit)

Patients with a positive anti-andexanet antibody response at the Day 30 visit should have additional follow up to approximately 120 days post-randomization.

3.3.1. Study Population

The study will enroll patients who have recently taken an oral FXa inhibitor (i.e., within 15 hours prior to randomization) with an acute intracranial bleeding episode. If a local anti-fXa activity obtained within 2 hours prior to consent is > 100 ng/mL for direct FXa inhibitors (apixaban, rivaroxaban or edoxaban), and performed as per standard of care, the patient may be enrolled if the time of last FXa inhibitor dose is > 15 hours or the time of the last dose is unknown, the patient should receive the high andexanet dosing regimen.

Due to their anatomic location and spatial constraints, intracerebral bleeds have a markedly poor prognosis, even in relationship to other major bleeding events [1]. Within the intracerebral hemorrhage population, it is appropriate to identify those patients at greatest risk for hematoma expansion, as this event is associated with poor clinical outcomes [5]. To this end, it is well appreciated that a shorter time interval between the onset of symptoms and clinical presentation is associated with an increased risk of hematoma expansion, with the greatest risk within the first 3 hours after symptom onset [13]. While the course of an intracerebral hemorrhage event in the

setting of therapeutic FXa inhibition is not fully known, a recent study reported a 38% incidence of hematoma expansion at a median follow-up time of 21 hours after presentation [14], suggesting that bleeding continues to occur throughout the first 24 hours. Thus, to ensure that enrolled patients are at risk for hematoma expansion, potential candidates will be excluded if the time from symptom onset to the baseline scan is greater than 6 hours.

It is important to note that andexanet does not directly repair bleeding lesions – it restores normal coagulative mechanisms in patients with acquired coagulopathy due to their anticoagulated state. Therefore, it is possible that certain defects, perhaps by virtue of their size, flow rate, or other coagulopathic mechanisms (e.g., platelet dysfunction), may not be amenable to anticoagulant reversal alone. Because patients with such lesions are unlikely to benefit from andexanet, potential patients with a GCS score < 7, a NIHSS score > 35, or a hematoma volume ≤ 0.5 or ≥ 60 mL will be excluded from the study.

Importantly, to ensure that enrolled patients are experiencing major bleeding associated with therapeutic anticoagulation with FXa inhibitors, it would be ideal to determine anti-fXa activity at baseline. However, because: 1) local anti-fXa activity testing is not available at all hospitals; and 2) there is no standardized clinical assay for anti-fXa activity, it is not possible to use anti-fXa activity as a universal marker of anticoagulation for purposes of enrollment into the study. Therefore, as a surrogate for elevated anti-fXa activity, the eligibility criteria restrict enrollment to patients who received their last dose of FXa inhibitor within 15 hours prior to randomization. The 15-hour time-point was selected to enrich the study population with patients with anti-fXa activity levels within therapeutic ranges. However, if local anti-fXa results are available, they may be used to qualify a patient where the last dose of anti-FXa inhibitor is > 15 hours or unknown only if 1) the local anti-fXa activity is > 100 ng/mL for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban), and 2) the local anti-fXa activity level is obtained within 2 hours prior to consent, performed as part of standard of care. The samples for anti-fXa activity (as well as for thrombin generation) collected at baseline and post-baseline for later analysis at a central laboratory, are the samples that will be used for analysis of secondary and additional efficacy outcome measures.

3.3.2. 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 activity, anticoagulant free fraction, and thrombin generation. In this study, hemostatic efficacy is being studied as the primary efficacy outcome, while the reversal of anticoagulation is being investigated as the secondary efficacy outcome. The timing of all endpoints is anchored on randomization.

3.3.2.1. Hemostatic Efficacy

Because of the clinical importance of hematoma expansion, CT/MRI-based volumetric measurement is considered to be the most direct way to evaluate hemostatic efficacy and will

constitute the primary assessment of this endpoint. That said, it is acknowledged that an evaluation of clinical status is potentially important to better ascertain the global benefit of an intervention. In the acute phase, the best clinical measure of focal neurologic change is captured by the NIHSS (Appendix E). Accordingly, for the purposes of evaluating the primary endpoint, the NIHSS will be measured by blinded personnel at 12 hours following randomization.

In addition, another important clinical metric of efficacy is the durability of therapy. Therefore, the use of pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, fresh frozen plasma [FFP] and anti-inhibitor coagulant complex [e.g., FEIBA®]), whole blood (see Table 5), hemostatic therapies, or an intervention/surgery intended to treat the hematoma at any time between 3 and 12 hours after randomization will result in the patient being considered having poor/none hemostatic efficacy in both treatment groups.

Given the above considerations, the adjudication of hemostatic efficacy will be based on a combination of imaging and clinical findings (Appendix B). If a patient has an increase in hematoma volume > 35% from baseline at any time between the end of initial randomized treatment and 12 hours post-randomization, they will be considered to have poor/none hemostatic efficacy. Additionally, if a worsening from baseline in NIHSS score of +7 or more is observed at 12 hours, a patient will be considered to have poor/none hemostatic efficacy. Finally, if a patient receives rescue therapy (as delineated above), they will also be considered to have poor/none hemostatic efficacy. Overall, if a patient should meet any one of the above criteria, they will be considered to have "symptomatic hematoma expansion" (see Section 7.4).

3.3.2.2. Anti-fXa Activity

Anti-fXa activity was chosen as the most relevant pharmacodynamic (PD) marker to evaluate the biochemical reversal of anticoagulation based on several mechanistic and empiric observations:

- 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 [15, 16].
- Plasma concentration of a FXa inhibitor correlates well with *ex vivo* anti-fXa activity [17, 18].
- The unbound plasma concentration of apixaban but not total plasma concentration correlates with anti-fXa activity in patients 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 [19-21].
- In animal models of blood loss, decrease in the plasma free fraction of FXa inhibitor and/or anti-fXa activity correlates with reduction in blood loss [15, 22].

- In patients with intracerebral bleeding while anticoagulated with FXa inhibitors, there was a strong positive association between baseline anti-fXa activity and the later occurrence of hematoma expansion [8].

3.3.3. Rationale for the Dose Regimen of Andexanet

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 of 480 mg at 4 mg/min.
- High dose: 800 mg IV bolus followed by a continuous infusion of 960 mg 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 4.

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 pharmacokinetic (PK)-PD model that predicted the time at which equivalent anti-fXa activity reversal and thrombin generation normalization would be achieved.

In addition to the above, the doses for this study (18-513) were shown to substantially reduce anti-fXa activity and increase thrombin generation in a Phase 3b/4 study where andexanet was given to patients receiving a FXa inhibitor who had acute major bleeding (Study 14-505 [ANNEXA-4]).

3.4. Safety Plan and Monitoring

The study will be conducted in patients who, by virtue of their condition, will typically be in acute care settings such as intensive care units and EDs. It is anticipated that patients with acute intracranial bleeding will remain hospitalized for well over 12 hours, the timeframe for the primary efficacy evaluations. During the first 24 hours after randomization (Study Day 1), AEs, vital signs, clinical neurologic testing, and brain imaging will be performed to monitor safety. If a patient has a clinically significant, new or worsening, focal or global neurologic deficit relative to baseline (e.g., an increase from baseline in the NIHSS score of 5 or greater), that is not readily explainable by an alternate etiology (e.g., sedatives, infection), Investigators will be requested to

pursue additional brain imaging. Investigators will also be allowed to scan patients for any medically indicated reason at their discretion.

After Study Day 1, all patients will be followed for AEs (including TEs) through the Day 30 visit. Survival status will be documented through Day 30, and the cause and date/time of death will be recorded, if applicable. Finally, patients will be assessed for antibodies to FX, FXa, and andexanet at the Day 30 visit. If a patient has a positive anti-andexanet antibody response at the Day 30 visit, they will return for a follow up anti-andexanet antibody test approximately 120 days after randomization, or within 30 days of when the positive test is made known to the Investigator, whichever is later.

Whether or not patients remain in the hospital, they will undergo the Study Day 2, Day 3, Day 7 (phone call), Day 14 (phone call), and Day 30, and Day 120 (as applicable) Follow-up visits to assess outcomes.

The independent EAC, in addition to adjudicating the primary efficacy endpoint, will also adjudicate all potential TEs using pre-defined criteria as described in the Adjudication Charter, as well as AESI and deaths. In addition, the independent DSMB will be empowered to recommend modifying or stopping the trial for safety reasons if warranted.

3.5. Benefit and Risk Assessment

FXa inhibitors are a significant therapeutic advance for several indications. However, a significant risk of anticoagulation with FXa inhibitors is the prospect of uncontrolled major bleeding. Patients enrolled in this study will have had an acute intracerebral bleeding episode in the setting of recent use of an FXa inhibitor. These bleeding episodes may be life-threatening, result in severe organ compromise, and/or prove fatal without rapid control of bleeding and resuscitative measures. Andexanet may be beneficial in reversing anticoagulation and, thus, removing anticoagulation as a contributor to the ongoing bleeding. In addition to any personal benefit to individual patients, there is a potential benefit to all current and future patients treated with andexanet (and, more generally, all patients taking FXa inhibitors) from the insights gained through this clinical study. The risks of study participation involve the risk of experiencing an AE related to andexanet or to the study procedures. To date, no major safety issues directly attributable to andexanet have definitively emerged in clinical studies. However, whenever chronic anticoagulation is reversed in patients with an indication to receive it, the risk of TEs is increased [23-25]. 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 weigh the risk of re-bleeding against the risk of thrombosis when considering whether to resume anticoagulation for the patient.

Some patients enrolled in this study will receive current usual care therapies for their acute intracerebral bleeding. While it could be reasonably argued that, in a critically ill bleeding patient, denial of use of an agent conditionally proven to rapidly reverse anti-fXa activity is unethical in a clinical setting where it is commercially available, it should be noted that, at present: 1) it is not definitively known if anti-fXa reversal is associated with clinical benefit; and 2) the potential risks of rapid reversal, including the risks directly attributable to andexanet, are not well defined.

Enrolled patients will have additional blood samples taken for assessment of various biomarkers of coagulation status, but the additional blood loss from phlebotomy will be minimal. The results of several of these blood tests, as well as other assessments associated with the study (e.g., imaging, physical exams, and clinical status metrics) will provide data that may allow Investigators to positively influence management of enrolled patients. Additionally, the results of the study will benefit patients with FXa inhibitor-induced acute intracerebral bleeding generally by gaining detailed insights into the natural history of this condition.

Based on the above considerations, the potential risks to patients in this study are justifiable and balanced by the potential benefits.

3.5.1. COVID-19

3.5.1.1. Vaccination

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

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination.

3.5.1.2. Potential Risks and Mitigation Measures

Acute intracerebral hemorrhage can cause irreversible morbidity and even mortality if untreated. As such, and because existing treatment options may be less effective than andexanet, the benefit a participant may receive from joining this investigational study is potentially significant. The potential risks identified and mitigation measures put in place in light of the COVID-19 pandemic are provided in Appendix F. The site Investigator will balance the risk/benefit considerations in the study participant taking these factors into account.

4.0 SELECTION OF STUDY POPULATION AND CRITERIA FOR WITHDRAWAL

4.1. Inclusion Criteria

To be eligible for study enrollment, potential study patients must satisfy all of the following inclusion criteria:

1. Written informed consent. Either the patient or his or her legally authorized representative (LAR) if permissible by local or regional laws and regulations has been adequately informed of the nature and risks of the study and has given written informed consent prior to Screening.
    - Deferred consent procedure is allowed where approved by local ethics committees. In cases of deferred consent, the time of the study physician's documented decision to include the patient into the study will serve as "time of consent" with respect to protocol-specific procedures.
    - In all cases where the patient does not sign informed consent prior to study entry, informed consent from the patient (or LAR) will be obtained as soon as realistically possible after inclusion in the trial and in accordance with the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP), the EU General Data Protection Regulation (GDPR), and national and local regulations.
2. Age ≥ 18 years old at the time of consent.
3. An acute intracerebral bleeding episode, defined as an estimated blood volume ≥ 0.5 to ≤ 60 mL acutely observed radiographically within the cerebrum. Patients may have extracerebral (e.g., subdural, subarachnoid, epidural) or extracranial (e.g., gastrointestinal, intraspinal) bleeding additionally, but the intracerebral hemorrhage must be considered the most clinically significant bleed at the time of enrollment.
4. Performance of a head CT or MRI scan demonstrating the intracerebral bleeding within 2 hours prior to randomization (the baseline scan may be repeated only once to meet this criterion).
5. Treatment with an oral FXa inhibitor (apixaban [last dose 2.5 mg or greater], rivaroxaban [last dose 10 mg or greater], or edoxaban [last dose 30 mg or greater]:
    - ≤ 15 hours prior to randomization.
    - > 15 hours prior to randomization or unknown time of last dose, only if 1) the local anti-fXa activity > 100 ng/mL for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban), as per standard of care, and 2) the local anti-fXa activity level is obtained within 2 hours prior to consent. Note: Patients enrolled in this manner should receive a high andexanet dosing regimen.

6. Time from bleeding symptom onset ≤ 6 hours prior to the baseline imaging scan. Time of trauma (if applicable) or time last seen normal may be used as surrogates for time of symptom onset. (If the baseline scan is repeated to meet Inclusion Criterion #4, the time from bleeding symptom onset must be ≤ 6 hours prior to the repeat baseline imaging scan.)
7. Female patients of childbearing potential and male patients with female partners of childbearing potential must follow protocol-specified guidance for avoiding pregnancy for 30 days after the last dose of study drug.
8. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential).
9. NIHSS score ≤ 35 at the time of consent.

4.2. Exclusion Criteria

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

1. Planned surgery, including Burr holes for hematoma drainage, within 12 hours after randomization. Minimally invasive surgery/procedures not directly related to the treatment of intracranial bleeding and that are not expected to significantly affect hematoma volume are allowed (e.g., Burr holes for intracranial pressure monitoring, endoscopy, bronchoscopy, central lines—Section 7.2, Section 7.3 and Appendix G).
2. GCS score < 7 at the time of consent. If a patient is intubated and/or sedated at the time of consent, they may be enrolled if it can be documented that they were intubated/sedated for non-neurologic reasons within 2 hours prior to consent.
3. *Purposefully left blank to align with the programmed database.*
4. Anticipation that the baseline and follow up brain scans will not be able to use the same imaging modalities (i.e., patients with a baseline CT scan should have a CT scan in follow up; similarly, for MRI).
5. Expected survival of less than 1 month (not related to the intracranial bleed).
6. Recent history (within 2 weeks) of a diagnosed TE or clinically relevant symptoms of the following:
    - Venous Thromboembolism (VTE: e.g., deep venous thrombosis, PE, cerebral venous thrombosis), myocardial infarction (MI), Disseminated Intravascular Coagulation (DIC), cerebral vascular accident, transient ischemic attack (TIA), acute coronary syndrome, or arterial systemic embolism (see Appendix H for DIC scoring algorithm).
7. Acute decompensated heart failure or cardiogenic shock at the time of randomization (see Appendix I for cardiogenic shock definition).

8. Severe sepsis or septic shock at the time of randomization (see Appendix I for sepsis definition).
9. The patient is a pregnant or lactating female.
10. Receipt of any of the following drugs or blood products within 7 days prior to consent:
    a. VKA (e.g., warfarin).
    b. Dabigatran.
    c. PCC (e.g., KCentra®) or rfVIIa (e.g., NovoSeven®), or anti-inhibitor coagulant complex (e.g., FEIBA®), FFP, and whole blood.
11. Past use of andexanet (or planned use of commercial andexanet).
12. Treatment with an investigational drug < 30 days prior to consent.
13. Any tumor-related bleeding.
14. Known hypersensitivity to any component of andexanet.

4.3. Criteria for Discontinuation from the Study

A patient may elect to discontinue participation in the study at any time. However, all efforts must be made to follow patients for the full duration of the study and to encourage all patients to complete the Day 30, and Day 120 (as applicable) contact.

If patients cannot or will not return for visits, the Investigator (or their designee) should attempt to contact them by telephone or other means; those who cannot be contacted should be considered lost to follow-up.

Reasons for all study withdrawals will be recorded. If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this request in the site study records.

Patients who discontinue study procedures for reasons other than withdrawal of consent can still have Day 30 mortality status collected.

4.4. Criteria for Discontinuation of Andexanet

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

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

Patients who discontinue study drug should still continue in the study. Patients who discontinue the study after receiving any amount of andexanet should undergo all follow-up safety procedures.

Reasons for all discontinuations of andexanet will be recorded.

4.5. Patient Replacement

Patients who are discontinued prematurely from the study will not be replaced. The study will continue to enroll patients until approximately 900 patients have been randomized.

4.6. Study Completion

Study completion for each patient is defined as completion of the Day 30 visit or, at a minimum, the time at which Day 30 mortality status is recorded. For patients with a positive anti-andexanet antibody response at the Day 30 visit, study completion is defined as completion of the follow-up visit approximately 120 days post-randomization, or within 30 days of when the positive test is made known to the Investigator, whichever is later.

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

In some countries, “study completion” may also be considered the same as “end of trial.”

4.7. End of the Trial

The end of the trial is defined as the last visit of the last patient in the trial. For patients who have a positive anti-andexanet antibody response at the Day 30 visit, the follow-up visit for an anti-andexanet antibody test approximately 120 days after randomization, or within 30 days of when the positive test is made known to the Investigator, whichever is later, will be considered their last study visit.

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 9.0.

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

5.1.1. Screening and Enrollment

Patients will be considered to be in screening once the ICF has been signed. Patients will be considered enrolled once they are randomized. Patients for whom the ICF is signed, but are ultimately not randomized, will be considered screen failures.

Laboratory assessments or procedures performed per standard of care at presentation of acute illness, but before signing of informed consent, may be used to assess eligibility.

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 withdraws consent from the study before the Day 30 Follow-Up 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 (if patient withdraws from the study prior to the 12-hour time-point).

- Modified Rankin Score /scale.
- EQ-5D.
- Survival status.
- Collect central laboratory specimens for antibodies (anti-andexanet, anti-fX, anti-fXa, and neutralizing antibodies).

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

6.0 DRUG SUPPLIES AND DOSING

6.1. Formulation

Andexanet is supplied in single-use, type I glass vials and contains 200 mg/vial as a lyophilized product for reconstitution for IV injection (at 10 mg/mL after reconstitution). The composition is listed in Table 2. 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 2: Reconstitution Volumes and Composition for Andexanet

Vial Contents	200 mg Vial
Reconstitution Volume	20.0 mL WFI

WFI = Water for injection

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

HCl = hydrogen chloride; QS = Quantum Sufficiat [Latin: as much as will suffice]

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 in Table 3. Time-points and windows for treatment procedures are outlined in Appendix A. Initiation of andexanet dosing should occur no later than 30 minutes after randomization and preferably within 2 hours of the baseline brain imaging scan. To accommodate dosing within 2 hours of the baseline scan closest to randomization, reconstitution of andexanet prior to randomization will be allowed.

Table 3: Dosing Paradigm for Andexanet

Dose	**Initial IV Bolus**	**Follow-on IV Infusion**
Low	400 mg at a target rate of 30 mg/min for ~15 minutes	480 mg at a target rate of 4 mg/min for 120 minutes
High	800 mg at a target rate of 30 mg/min for up to ~30 minutes	960 mg at a target rate of 8 mg/min for 120 minutes

IV = intravenous

The decision to administer a low or high dose will be governed by the dose regimens in Table 4:

Table 4: Andexanet Dose Regimens

FXa Inhibitor	FXa Inhibitor Last Dose [a]	Timing of FXa Inhibitor Last Dose before Andexanet Initiation		
		< 8 Hours	≥ 8 Hours	> 15 Hours or Unknown [b]
Rivaroxaban	10 mg	Low Dose	Low Dose	High Dose
	> 10 mg	High Dose		
Apixaban	≤ 5 mg	Low Dose		
	> 5 mg	High Dose		
Edoxaban	30 mg	Low Dose		
	> 30 mg	High Dose		

[a] This represents the last dose taken by the patient, not the total daily dose.

[b] ONLY if 1) the local anti-fXa activity > 100 ng/mL for direct fXa inhibitors (apixaban, rivaroxaban or edoxaban), and 2) the local anti-fXa activity level is obtained within 2 hours prior to consent and performed as per standard of care.

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.

The Investigator (or his or her designee) is required to confirm that appropriate temperature conditions were maintained during transit of the drug. Any temperature excursions and resolution of any temperature excursions prior to drug use must be reported within one business day. Any product complaints must also be reported within one business day. Please refer to the Pharmacy Manual for details.

6.4. Drug Accountability and Compliance

The dispensing pharmacist or designated qualified individual will write at least 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 either be destroyed at the site in accordance with approved written site procedures or returned to the Sponsor or its designee only after written authorization is obtained from the Sponsor or its designees. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 12.5 Retention of Data.

7.0 PRIOR AND CONCOMITANT MEDICATIONS AND TREATMENTS

7.1. Prior Medications and Treatments

Section 4.1 and Section 4.2 describe restrictions on prior medications and treatments.

Platelets and PRBCs are allowed at any time prior to screening.

The followed are not allowed within 7 days prior to consent:

- Vitamin K Antagonist (VKA) (e.g., warfarin)
- Dabigatran
- Prothrombin Complex Concentrate products (PCC, e.g., KCentra®) or recombinant factor VIIa (rfVIIa) (e.g., NovoSeven®), or anti-inhibitor coagulant complex (e.g., FEIBA®), FFP, and whole blood

Past use of commercial andexanet is not permitted, and treatment with an investigational drug < 30 days prior to consent is not permitted.

7.2. Concomitant Medications, Hemostatic, and Pro-coagulant Treatments

The use of concomitant medications and treatments, including surgeries, is summarized in Table 5 and detailed in the subsections below.

Table 5: Allowed Use of Concomitant Medications and Treatments

Concomitant Medication and Treatments	Allowed Use
Anticoagulants (e.g., direct thrombin inhibitors, FXa inhibitors, vitamin-K antagonists) and Antiplatelet Drugs (e.g., prasugrel, ticagrelor, clopidogrel, aspirin, NSAIDs)	• For both treatment groups, can be restarted at any time based on clinical judgment.
Platelets and PRBCs	• Patients in both groups may receive platelets and/or PRBC transfusions at any time. • Use of platelets or red blood cells will not have any bearing on hemostatic efficacy.
Pro-Coagulant Blood Products (pro-coagulant factor infusions [e.g., 3- or 4-factor PCC/activated PCC, recombinant fVIIa, plasma, FFP, FEIBA®], and whole blood)	• For patients randomized to usual care treatment, blood products may be administered within the initial 3-hour treatment window post-randomization per institutional/local practices and/or guidelines. • For patients randomized to andexanet, blood products may be administered if a patient is found to have hematoma expansion. • For both treatment groups, administration of blood products between 3 hours post-randomization and the 12-hour hemostatic efficacy evaluation will result in the patient being considered to have poor/none hemostatic efficacy.

Table 5: Allowed Use of Concomitant Medications and Treatments

Concomitant Medication and Treatments	Allowed Use
	• Misadministration of procoagulant blood products contrary to treatment allocation within 3 hours post-randomization (including andexanet in usual care arm) will be reviewed by EAC.
Hemostatic Agents (systemic anti-fibrinolytic [e.g., aminocaproic acid] and other systemic hemostatic agents)	• For patients randomized to usual care treatment, systemic hemostatic agents may be administered per institutional/local practices and/or guidelines. • For patients randomized to andexanet, local hemostatic agents and topical vasoconstrictors may be administered as clinically appropriate. • For both treatment groups, administration of systemic hemostatic agents (with the exception of tranexamic acid) between 3 hours post-randomization and the 12-hour hemostatic efficacy evaluation will result in the patient being considered to have poor/none hemostatic efficacy. • Administration of hemostatic agents within 3 hours post-randomization will be reviewed by EAC.
Diagnostic and Therapeutic Procedures, including Surgeries, for Bleeding (including Burr holes intended for hematoma expansion)	• For both treatment groups, planned minimally invasive procedures not directly related to treatment of the intracranial bleeding (e.g., endoscopy, bronchoscopy, central lines) may be performed without restrictions as deemed clinically appropriate. In addition, Burr holes are allowed at any time if they are indicated for placement of an intracranial pressure monitor, and not anticipated to drain any portion of hematoma volume. • For both treatment groups, performance of an unplanned rescue surgery or interventional procedure to treat the index hematoma in the event of clinical deterioration between 3 hours post-randomization and the 12-hour hemostatic efficacy evaluation will result in the patient being considered to have poor/none hemostatic efficacy. • Unplanned rescue procedures or surgery which could impact hematoma volume will be reviewed by EAC. • For both treatment groups, performance of a surgery or interventional procedure to treat the index hematoma or could impact hematoma volume within 3 hours post-randomization will be reviewed by EAC.

EAC = Endpoint Adjudication Committee; FEIBA = factor eight inhibitor bypass activity; FFP = fresh frozen plasma; fVIIa = factor VIIa; FXa = factor Xa; NSAIDS = nonsteroidal anti-inflammatory drugs; PCC = prothrombin complex concentrate; PRBC = packed red blood cell

7.2.1. Anticoagulants and Antiplatelet Drugs

Investigators may choose to re-start anticoagulants or antiplatelet drugs (including, but not limited to prasugrel, ticagrelor, clopidogrel, aspirin, and Non-Steroidal Anti-Inflammatory Drugs [NSAIDs]) at any time based on clinical judgment. If anticoagulants or antiplatelet agents are restarted during the study, the date, time, and agent(s) used should be recorded on the 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.

For both treatment groups, transfusion of platelets and/or PRBCs may be performed at any time without any bearing on the primary efficacy endpoint.

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

7.2.3. Procoagulant Blood Products

For patients randomized to usual care treatment, pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP, FEIBA®), and/or whole blood may be administered within the initial 3-hour treatment window post-randomization according to standard institutional/local practices and/or guidelines. If a patient is randomized to andexanet, Investigators may consider using pro-coagulant factor infusions, as listed above, if a patient is found to have hematoma expansion (i.e., a > 35% increase in volume from baseline) on either a protocol-driven or clinically-indicated scan. Otherwise, treatment with the above products is strongly discouraged, though not prohibited, during the entire 30-day observation period.

For both treatment groups, use of pro-coagulant factor infusions (e.g., 3- or 4-factor PCC/activated PCC, rfVIIa, plasma, FFP, FEIBA®) and/or whole blood between 3 hours after randomization and the 12-hour hemostatic efficacy evaluation measurements will result in the patient being considered to have poor/none hemostatic efficacy.

Misadministration of procoagulant blood products contrary to treatment allocation within 3 hours post-randomization (including andexanet in usual care arm) will be reviewed by EAC.

7.2.4. Hemostatic Agents

For patients randomized to usual care treatment, systemic anti-fibrinolytic (e.g., aminocaproic acid) and other systemic hemostatic agents may be administered according to standard institutional/local practices and/or guidelines. If a patient is randomized to andexanet, Investigators may consider using hemostatic agents, as listed above, if a patient is found to have hematoma expansion as delineated in Section 7.4. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

Similarly, for patients randomized to usual care treatment, local hemostatic agents (e.g., microfibrillar collagen and chitosan-containing products) and topical vasoconstrictors (e.g., epinephrine) may be used as deemed clinically appropriate. For patients randomized to andexanet, Investigators may consider using local hemostatic agents if a patient is found to have hematoma expansion. Otherwise, treatment with these agents is strongly discouraged, though not prohibited, during the entire 30-day observation period.

For both treatment groups, use of systemic hemostatic agents (with the exception of tranexamic acid) between 3 hours after randomization and the 12-hour hemostatic efficacy evaluation measurements will result in the patient being considered to have poor/none hemostatic efficacy. Administration of hemostatic agents within 3 hours post randomization will be reviewed by EAC.

Use and timing 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 at the time of randomization to undergo surgery or hematoma drainage procedures (including Burr holes intended for hematoma evacuation) within 12 hours after randomization are excluded from the study, though unplanned rescue procedures of this nature may be carried out post-randomization (see Section 4.2 for Exclusion Criteria).

Burr holes planned within 12 hours after randomization are allowed if they are indicated for placement of an intracranial pressure monitor, and not anticipated to drain any portion of hematoma volume. In addition, planned minimally invasive procedures not directly related to treatment of the intracranial bleeding (e.g., endoscopy, bronchoscopy, central lines—see Appendix G) may be performed without restrictions as deemed clinically appropriate.

Through the period of the primary efficacy assessment (12 hours after randomization), Investigators will be requested to pursue additional brain imaging (e.g., CT, MRI, cerebral angiogram) to evaluate for hematoma expansion (i.e., continued bleeding or re-bleeding) if clinically indicated. Patients will be re-scanned if they have a clinically significant new or worsening, focal or global, neurologic deficit relative to baseline (e.g., an increase from baseline in the NIHSS score of 5 or greater), that is not readily explainable by an alternate etiology (e.g., sedatives, infection). The new neurologic deficit can be discovered at any time following initial treatment through 12 hours after randomization. In addition, Investigators will be allowed to pursue additional brain imaging at any time for any medically appropriate reason.

For both treatment groups, performance of an unplanned rescue surgery or interventional procedure specifically indicated to treat the index hematoma in the event of clinical deterioration between 3 hours after randomization and the 12-hour hemostatic efficacy evaluation will result

in the patient being considered to have poor/none hemostatic efficacy. Unplanned rescue procedures or surgery which could impact hematoma volume will be reviewed by EAC.

For both treatment groups, performance of an unplanned rescue surgery or interventional procedure to treat the index hematoma or could impact hematoma volume within 3 hours post-randomization will be reviewed by EAC.

The use and timing of procedures for diagnosis and management of bleeding should be recorded on the CRFs.

7.4. Continued Bleeding, Re-bleeding, and Rescue Therapy

In this study, there is potential for patients to experience continued bleeding and/or re-bleeding after therapy (be it usual care or andexanet). That said, because they represent the two potential mechanisms for hematoma expansion, continuous bleeding and re-bleeding should be considered within the broader scope of hematoma expansion. That is, patients with continuous bleeding and patients with re-bleeding represent subsets of patients with hematoma expansion. Therefore, when considering the use of rescue therapy for continued bleeding or re-bleeding, Investigators should consider whether the patient has evidence of hematoma expansion (defined as any increase from baseline in hematoma volume greater than 35%).

For all patients, while Investigators are strongly encouraged to perform diagnostic imaging if continued or recurrent bleeding is suspected, any therapy (other than andexanet) may be used at any time to address continued or recurrent bleeding. No andexanet dosing (for the usual care group) or re-dosing (for the andexanet group) is allowed.

For all patients, any blood product (excluding PRBCs and platelets), pro-coagulant factor infusions, or systemic hemostatic therapy (except tranexamic acid) specifically intended to address continued or recurrent bleeding (as listed in Section 7.2.2 and Section 7.2.4), initiated at least 3 hours after randomization but before the 12-hour hemostatic efficacy assessment, will be considered rescue therapy. Any patient receiving such systemic rescue therapy will be considered a treatment failure (i.e., poor/none hemostatic efficacy).

Additionally, any unplanned rescue surgical procedure specifically intended to treat the hematoma at any time between 3 hours post-randomization and the 12-hour hemostatic efficacy evaluation measurements will result in the patient being considered to have poor/none hemostatic efficacy.

7.5. Infusion Reactions

As discussed in the IB, mild to moderate infusion reactions were reported in healthy subjects who received andexanet and rarely occurred in bleeding patients who were treated in a Phase 3b/4 study. 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.

7.6. Thrombotic Events

Patients will be monitored carefully for signs and symptoms of TEs (i.e., strokes, TIAs, MIs, DVTs, PEs, arterial systemic embolisms) throughout the course of the study. In the event that the Investigator suspects a TE, it is expected that an appropriate evaluation will be performed (e.g., head CT, electrocardiogram [ECG]/cardiac enzymes, lower extremity ultrasound, pulmonary vascular imaging). Investigators are requested to consult the guidance listed in Appendix K when considering whether an event should be submitted for adjudication. Ongoing periodic review of AEs during the conduct phase of the study, assessing for potential TEs to be submitted for adjudication, will also be conducted by the Sponsor.

8.0 ADVERSE EVENT REPORTING

8.1. Adverse Event Definitions

According to the ICH guideline for GCP, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution to study treatment or procedure. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For the purposes of this study, a Treatment-Emergent AE (TEAE) is one that occurs at any time following treatment initiation.

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 or recurrence of an intermittent medical condition not present at baseline]).
- All reactions from study drug, abuse of drug, withdrawal phenomena, sensitivity or toxicity to study drug.
- Any complication or injury resulting from a study-specific procedure (e.g., thrombophlebitis from an IV line).
- 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, represent a worsening from baseline, and meet any of the below-listed criteria 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 an SAE, or
  - Results in study discontinuation.

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.

8.1.1. Study-specific Exceptions to Adverse Event/Serious Adverse Event Reporting

For the purposes of this trial, hematoma expansion or intracerebral bleeding and associated neurological deterioration that occurs within the first 12 hours post-randomization will not be regarded as an AE or SAE except when there is evidence suggesting a causal relationship between the drug and the event. Such events will be captured on the electronic Case Report Form (eCRF) and in the database as outcomes only; they will also be waived from unblinding and exempt from expedited reporting.

8.2. Serious Adverse Event Definition

An SAE is any AE, occurring 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 MI; the event itself, however, may be of relatively minor medical significance (such as severe headache). This is **not** the same as "serious," which is based on 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.

8.2.1. Regulatory Reporting Requirements for Serious Adverse Events

- The Investigator must notify the Sponsor of an SAE within 24 hours of the first awareness of the event.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and Investigators.
- The Council for International Organizations of Medical Sciences (CIOMS) or MedWatch reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) (Section 8.3) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary. The Sponsor's procedures for the reporting of SUSARs are in accordance with United States Title 21 Code of Federal Regulations (CFR)312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries as well as IRBs/IECs where applicable.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and acknowledge the report and notify the IRB/IEC, if appropriate, according to local requirements.

8.3. Suspected Unexpected Serious Adverse Reactions

A SUSAR is an event that is assessed as serious by the Investigator and/or the Sponsor that is not listed in the Reference Safety Information of the IB and has been assessed as having at least a reasonable possibility of being related to the investigational medicinal product by the Investigator and/or the Sponsor.

The Sponsor has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.

SUSARs will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable. The Sponsor is required to take the following actions:

- In the case of SUSARs with an outcome of death or that are life-threatening, the Sponsor is required to report the event within 7 days. SUSARs with any of the other outcomes are required to be reported to regulators within 15 days.
- Inform all Investigators of the SUSAR.

8.4. Adverse Events of Special Interest

Thrombotic or embolic events of any severity are AESI and should be reported as non-serious AEs or as SAEs (if appropriate) within 24 hours after the Investigator is made aware of them, as described in Section 8.8.

The Investigator will assess relationship of the AESI to andexanet as described in Section 8.5. In addition, the DSMB will periodically consider whether the occurrence of AESIs (whether related or not) warrant changes to the study (see Section 10.6.2 and the DSMB Charter).

8.5. Assessment of Causal Relationship

The Investigator should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the randomized treatment (andexanet or usual care). For each AE/SAE, the Investigator must document in the medical notes that they have reviewed the AE/SAE and have provided an assessment of causality.

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

Related

The AE:

- Follows a reasonable temporal sequence from the time the randomized treatment was administered; and/or
- Follows a known response pattern to the randomized treatment; and
- Does not have a likely alternative etiology.

Unrelated

The AE:

- Does not follow a reasonable temporal sequence from the time the randomized treatment was administered; and
- Was most likely produced by other factors, such as the patient's clinical state, therapeutic intervention, or concomitant therapy; or
- Was clearly and incontrovertibly due only to extraneous causes (e.g., the patient's clinical state, therapeutic intervention other than bleeding control, or concomitant therapy other than the randomized treatment) and does not meet the criteria listed above under *"Related."*

An AE with causal relationship not initially determined will require urgent follow-up to assign causality. Additionally, lack of efficacy does not necessarily constitute relatedness to the randomized therapy.

8.6. 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 tolerated
Moderate	Discomfort enough to cause interference with normal daily activities
Severe	Inability to perform normal daily activities

8.7. Adverse Event Reporting

For all patients, the AE reporting period starts with the signing of the ICF and continues through the Day 30 Follow-up visit. For patients who have a positive anti-andexanet antibody response at the Day 30 visit, the AE reporting period will extend through their Day 120 follow-up visit.

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 Day 30 Follow-up visit. All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded and reported on the appropriate CRF through the Day 30 Follow-up visit.

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

After informed consent has been signed but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until 30 days after the last dose of the study treatment. After this reporting period, the Investigator is not required to actively monitor patients for AEs; however, the Sponsor should be notified if the Investigator becomes aware of any post-study SAEs that are believed to be related to prior study treatment.

All SAEs and AESIs (see Section 8.4) must be reported by the Investigator by sending the SAE Form and any pertinent source documents and recording the SAE on the AE CRF, 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. Any follow-up information on a previously reported SAE or AESI should be sent promptly by the Investigator within 24 hours from the point in time when the Investigator becomes aware of it), or as requested by the Sponsor or its designee.

The Sponsor will immediately notify the Investigator about important safety or toxicology information, including neutralizing antibodies against FX or FXa identified in a patient treated with andexanet in any clinical study, as it becomes available. It is the responsibility of the Investigator to promptly notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious adverse drug reactions (implied causal relationship to study treatment) involving risk to human subjects, in accordance with the applicable policies. Certain countries (e.g., the Netherlands) require the Sponsor to notify the IRB/IEC about new and relevant safety information regarding the study drug, including serious adverse drug reactions involving risk to human subjects. An unexpected event is one that is not listed by nature or severity in the Reference Safety Information.

8.9. Contraception

Andexanet is not expected to have reproductive or developmental toxicity based on the following: 1) andexanet is intended for single-dose administration and, therefore, has limited potential for reproductive or developmental toxicity; 2) andexanet is a biotechnology-derived protein that is a modification of an endogenous protein in the coagulation cascade (FXa); 3) andexanet has a very short half-life (1- to 2-hour effective half-life); and 4) andexanet was designed as a universal antidote for FXa inhibitors, which are prescribed primarily in elderly patient populations that are not of reproductive capacity. Andexanet is not expected to interact with hormone contraception.

Nevertheless, one of the following highly effective birth control methods is recommended for female patients of childbearing potential for the entire duration of the trial and for at least 1 month after study drug administration:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Intravaginal
    - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Injectable
    - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Successfully vasectomized partner
- Sexual abstinence

Male patients with female sexual partners who are pregnant or of childbearing potential must use one acceptable method of contraception, including a barrier method (e.g., condom), for the entire duration of the study and for at least 1 month following study drug administration. Also, male patients must refrain from attempting to father a child or donating sperm for 1 month following study drug administration. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Acceptable birth control methods are those that result in a failure rate of more than 1% per year. These methods include progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; male or female condom with or without spermicide

cap; and diaphragm or sponge with spermicide. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable but are not highly effective birth control methods.

8.9.1. 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. The Sponsor must, in turn, also be notified by the Investigator immediately (no more than 24 hours after learning of the pregnancy) by completing a Pregnancy CRF and a Pregnancy/Breastfeeding Reporting and Outcome form. In the event a female 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 immediately report to the Sponsor the abnormal fetal outcome on an SAE form.

9.0 STUDY ASSESSMENTS

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

9.1. Efficacy Assessments

9.1.1. Effective Hemostasis

Effective hemostasis is a composite endpoint based on image evaluation (CT or MRI), NIHSS score, and use of rescue therapy. Imaging is to be performed at baseline and approximately 12 hours post-randomization, and should utilize a consistent imaging modality for both time-points to minimize technical discrepancy (i.e., CT or MRI scan). However, additional imaging may be performed at any time during the study per Investigator discretion and should be considered in the case of clinical deterioration. NIHSS evaluation (blinded or unblinded) to inform hemostatic efficacy will be performed at baseline (prior to randomization) and at 2 hours, 3 hours, 6 hours, and 72 hours post-randomization. Blinded NIHSS evaluation will occur at 12 hours and 24 hours post-randomization to minimize bias. As with brain imaging, additional assessments may be performed at any time. Use of rescue therapy (including procedures intended to treat the hematoma), as defined in Section 7.2, Section 7.3, and Section 7.4, between 3 hours and 12 hours following randomization will be considered a treatment failure (i.e., poor/none hemostatic efficacy).

9.1.2. Anti-fXa Activity

Anti-fXa activity will be measured from plasma samples to assess the anticoagulant status of FXa inhibitors using a modified chromogenic assay performed at a Central Laboratory. Anti-fXa activity will be evaluated at baseline, and at 1- and 2-hours post-randomization.

9.1.3. Thrombin Generation

Thrombin generation will be measured from plasma samples to assess the anticoagulant effect of FXa inhibitors. Tissue factor-dependent thrombin generation will be performed at a Central Laboratory. Five parameters related to thrombin generation are measured: 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. Thrombin generation will be assessed at baseline, and at 1- and 12-hours post-randomization.

9.1.4. Glasgow Coma Scale (GCS) Score

GCS evaluation (blinded or unblinded) will be performed at baseline (prior to randomization) and at 2 hours, 3 hours, 6 hours and 72 hours post-randomization. Blinded GCS evaluation will occur at 12 hours and 24 hours post-randomization.

9.1.5. Modified Rankin Scale

An mRS score will be obtained at baseline (pre-morbid), at 30 days post-randomization or at the Early Termination visit. If the baseline mRS is unavailable during screening, the mRS can be collected from either the patient, relative, care giver, or LAR at a post-randomization timepoint as long as the mRS reflects the patient's pre-morbid (i.e., pre- ICrH) neurological status. The pre-morbid mRS score should reflect the patient's neurological status prior to acute illness. The utility-weighted mRS (uw-mRS) is a quality-of-life measure ensuring that the mRS score reflects both treatment effect and patient perception. In the uw-mRS, utilities based on the EuroQol Group 5-Dimension (EQ-5D) questionnaire values are assigned to the mRS health states.

9.1.6. EQ-5D (EuroQol-5 Dimension)

A five-dimension health-related quality of life measure for clinical and economic appraisal will be obtained at 30 days post-randomization or at the Early Termination visit.

9.2. Safety Assessments (other than Adverse Events)

9.2.1. Vital Signs, Height, and Weight

Vital signs include temperature, SBP, Diastolic Blood Pressure (DBP), Heart Rate, and Respiratory Rate.

Height and weight will be recorded at screening and baseline. If it is not possible to measure height or weight, a reported height or weight, or a recent height or weight from the medical record is acceptable.

9.2.2. Clinical Laboratory Testing

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

The following assays will be performed at the Local Laboratory (as available):

- Hematology: hemoglobin, hematocrit, White Blood Cell (WBC) count, platelet count, WBC differential
- Coagulation: International Normalized Ratio (INR)
- Serum Chemistry: sodium, potassium, chloride, carbon dioxide (bicarbonate), glucose, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, calcium, phosphorus, and total, direct, and indirect bilirubin
- Serum or urine pregnancy test (in females of childbearing potential; see Appendix J)
- Anti-fXa activity (for patients treated with an oral FXa inhibitor > 15 hours prior to randomization or unknown time of last dose). Note: Measurements of anti-fXa

activity after initiation of andexanet are discouraged because of assay interference with andexanet. Please consult the Laboratory Manual for further details.

Local Laboratory assays of hematology, coagulation, and serum chemistry are not required for the purpose of eligibility. However, complete panels should not be missed at screening/baseline because these assays inform the investigator of suitability of the patient for the study (e.g., multiorgan failure, metabolic or hematological abnormalities).

The following assays will be performed at a Central Laboratory:

- Anti-fXa activity (Note: evaluation of the secondary efficacy endpoint will use only central, and not local, anti-fXa activity)
- Antibodies to FX, FXa, and andexanet
- Neutralizing antibodies to FX, FXa, and andexanet
- Thrombin generation

The multiple samples collected within a narrow window of time (±15 min) from baseline through to the first 2 to 3 hours are critical for the Central Lab's assessment of andexanet activity.

9.2.2.1. Exploratory Biomarker Assessments

Samples for tissue factor pathway inhibitor (TFPI) activity or other future exploratory biomarker research will also be obtained at selected time-points (see Appendix A).

TFPI, an endogenous inhibitor of fXa and known to interact with andexanet, will be measured using Antichrome®-TFPI Chromogenic assay at a Central Laboratory. TFPI will be evaluated at baseline, 1-, 2-, and 12-hours post-randomization and at the 30 day follow-up visit.

10.0 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.

10.1. General Considerations

During the conduct of the study, the Sponsor and Investigators will be blinded to the aggregated efficacy and safety summaries. Also, all unblinded analyses that are required to support the DSMB will be performed by an independent unblinded statistician. These analyses will be performed under the direction of the DSMB according to the Statistical Analysis Plan (SAP) and the DSMB Charter. The results of these unblinded analyses will not be available to the Sponsor or Investigators until after database lock, unless the DSMB recommends early termination of the trial.

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

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

All efficacy hypothesis tests will be 2-sided and performed at the 0.05 significance level. Adjustments for the overall type I error for the planned interim efficacy analysis are described in Section 10.7.

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 efficacy and safety endpoint parameters will be summarized descriptively.

10.2. Randomization

This is a prospective, randomized, open-label study, with blinded assessment of efficacy and safety (TEs and deaths) outcomes by the independent EAC. Patients will be randomized 1:1 to andexanet or usual care, stratified by the Investigator's intended-usual-care-agent, determined on a patient-by-patient basis, as well as time from symptom onset to baseline imaging scan.

10.3. Determination of Sample Size

Hemostatic efficacy was reported by Sarode et al [7] as 58.3% (95% CI 27.7, 84.8) and 41.7% (95% CI 15.2, 72.3) for a small sample of ICrH patients receiving FFP and 4F-PCC, respectively. For the overall population, the reported hemostatic efficacy was 65.4% (95% CI 55.4, 74.4) and 72.4% (95% CI 62.5, 81.0) for patients receiving FFP and 4F-PCC, respectively.

Also, in a study evaluating the efficacy of idarucizumab to reverse the effect of dabigatran [11, 26], the proportion of the overall patient population with an Investigator-assessed time to hemostasis less than 24 hours can be estimated to be approximately 66% (95% CI 59, 73). In addition, in 2 studies evaluating the efficacy of 4F-PCC in patients with FXa inhibitor-related major bleeding, hemostatic efficacy was reported as 69.1% (95% CI 58, 79) [27] and 84.8% (95% CI 74, 93) [28]. Gerner et al [8] investigated a total of 190 patients with intracerebral bleeding over a 5-year period treated with dabigatran (n=22), rivaroxaban (n=142), and apixaban (n=26). For these patients, the rate of hematoma expansion (defined as an increase from baseline of 33% or greater on follow up imaging) was observed to be 35% (therefore, 65% of patients did not have hematoma expansion). Finally, in a retrospective observational cohort of ICrH patients receiving PCCs, hemostatic efficacy was noted to be 81.8% in 433 efficacy evaluable patients [29].

For bleeding patients treated with andexanet, the FXa inhibitor reversal agent being evaluated in the current study, results from 477 patients enrolled in a Phase 3b/4 single arm, open-label study (ANNEXA-4) as of 30 June 2020 showed an effective hemostasis rate of 79% (95% CI of 74, 84) for 244 efficacy-evaluable patients with ICrH. Overall, for a total of 340 efficacy evaluable patients with all types of bleeding, the rate of effective hemostasis was 80% (95% CI of 75, 84).

The primary objective of this study is to compare the rate of effective hemostasis between andexanet and usual care in intracerebral hemorrhage patients. The statistical significance of the comparison will be evaluated by a two-sided test with the null hypothesis of no difference. Based on the hemostatic efficacy results discussed above, it is assumed that the rate of effective hemostasis in this study will be approximately 70% and 80% for patients treated with usual care and andexanet, respectively. The 10% absolute difference also represents a 33% risk reduction of not achieving effective hemostasis by andexanet as compared to usual care, such a magnitude is considered clinically meaningful. After accounting for early discontinuation rate and one interim analysis, it is estimated that a total sample size of approximately 900 patients (i.e., 450 patients per group) will have approximately 90% power to detect a 10% absolute difference between andexanet and usual care in the rate of effective hemostasis at a 0.05 two-sided overall significance level.

10.4. Analysis Populations

10.4.1. Safety Analysis Population

The safety analysis population will consist of all randomized patients who received the study treatment (andexanet or usual care) and analyzed according to the actual treatment received.

10.4.2. Efficacy Analysis Population

Intent-to-Treat Population (ITT): The ITT Population will include all randomized patients according to the randomized treatment. Participants who are randomized without signing the consent form throughout the study will not be included in the ITT set.

Per-Protocol Population (PP): The PP Population will include all patients in the ITT population who did not have important protocol deviations which impact the primary efficacy assessment.

The full definition of the PP set is provided in the SAP.

10.4.3. Patient Disposition

Patient disposition, including total screened, enrolled, randomized, early terminations, and withdrawals, will be presented by treatment assignment. In addition, a listing will be providing with the reasons for screen failures and study discontinuations.

10.4.4. 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.

10.4.5. Treatment Compliance

Patient compliance with the assigned treatment will not be evaluated since all procedures are performed in the hospital by a trained professional (for andexanet, any dose modifications will also be recorded and presented). However, lack of compliance or deviation from the study required evaluations will be listed.

10.5. Efficacy Endpoints and Analyses

10.5.1. Population

The primary, secondary, and additional efficacy endpoints will be analyzed using the ITT population.

10.5.2. Definitions

Hemostatic efficacy will be determined by the blinded EAC. Cases will be primarily determined to have effective hemostasis (i.e., a rating of “good” or “excellent”) or not (i.e., a rating of “poor/none”) based on pre-specified criteria documented in the Adjudication Charter and summarized in Appendix B.

For biomarker endpoints, the baseline measurement will be the most recent value drawn within 120 minutes prior to randomization. Any baseline measurement collected greater than 120 minutes prior to randomization will be considered out of window.

10.5.3. Efficacy Endpoints

10.5.3.1. Primary Efficacy Endpoint

The primary efficacy endpoint is based on the achievement of effective hemostasis 12 hours post-randomization, as determined by the blinded EAC, based on pre-specified criteria documented in the Adjudication Charter (see Appendix B).

Effective hemostasis will be further defined as:

- 1 = for patients with hemostatic efficacy rated by the EAC as excellent or good, and
- 0 = for patients with hemostatic efficacy rated by the EAC as poor/none.

For a patient to have excellent or good hemostatic efficacy, he or she must meet all of the following criteria:

- NIHSS score of less than +7 point change from the baseline score at 12 hours post-randomization.
- No greater than 35% increase from baseline in hematoma volume within 12 hours post-randomization.
- Has not received rescue therapy (as defined in Section 7.2, Section 7.3, and Section 7.4) between 3 and 12 hours post-randomization

If data supporting either the imaging or clinical components of the adjudication of hemostatic efficacy are missing, out-of-window, uninterpretable or confounded (e.g., intubation or sedation), cases will be referred for external adjudication by EAC. Procoagulant blood products administered within 3 hours post-randomization to patients randomized to andexanet will be reviewed by EAC to determine if they were related to clinical or administrative reasons. Surgeries or procedures impacting hematoma volume within 3 hours post-randomization will also be reviewed by EAC to determine if related to clinical or administrative reasons (see Section 7.2, Section 7.3, and Section 7.4).

Cases where it is determined that there is insufficient information, or when it is not otherwise possible to properly assess the effect of treatment, will be further classified by the EAC as ‘non-evaluable due to administrative reasons’ (e.g., follow-up scan not available/ performed/ interpretable, patient transferred to another facility for administrative purposes) or ‘non-evaluable due to clinical reasons’ (e.g., patient died, patient had unplanned surgery draining hematoma).

All ITT patients will be included in the primary analysis. Patients with non-evaluable hemostatic efficacy due to clinical reasons will be treated as treatment failures (similar to patients with poor/none hemostatic efficacy). Both non-evaluable subjects due to administrative and clinical reasons will be included in the denominator for primary efficacy analysis.

To evaluate the robustness of the primary efficacy results, sensitivity analyses will be performed. Further details will be provided in the SAP.

10.5.3.2. Secondary Efficacy Endpoint

The secondary efficacy endpoint is:

- Percent change from baseline to nadir in anti-fXa activity during the first 2 hours post-randomization.

Missing data for anti-fXa activity will be imputed using the multiple imputation method described by Rubin (1976) [30].

10.5.3.3. Additional Efficacy Endpoints

The additional efficacy endpoints include the following:

- Change from baseline in thrombin generation parameters (with ETP as the primary measure) obtained at 1 and 12 hours post-randomization.
- Proportion of neurologic deterioration, as defined by NIHSS increase ≥ 4 or a GCS score decrease ≥ 2 at 24 hours post-randomization versus baseline.
- Change from baseline in mRS score at 30 days post-randomization.
- Change from baseline in NIHSS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization.
- Change from baseline GCS score obtained at 2, 3, 6, 12, 24, and 72 hours post-randomization.
- Proportion of patients with a ≥ 7-point increase from baseline in NIHSS at 12 hours post-randomization.
- Hemostatic efficacy evaluated using only imaging parameters.
- Proportion of patients receiving rescue therapy between 3 and 12 hours post-randomization.
- Correlation analysis between anti-fXa activity and the achievement of hemostatic efficacy.
- Health-related quality of life as assessed by the EQ-5D questionnaire at 30 days post-randomization.
- UW-mRS score at 30 days post-randomization.

10.5.4. Statistical Methodology for Efficacy Endpoint Analyses

10.5.4.1. Control of Family-Wise Error Rate

A combination of a hierarchical testing procedure and Hochberg Procedure will be used to test the primary and the secondary endpoint.

For the interim analysis, a hierarchical testing procedure will be used to test the primary and the secondary endpoint. The primary endpoint will be tested at an alpha level of 0.031. If the primary endpoint is statistically significant, the secondary endpoint will be tested at an alpha level of 0.031.

The final analysis is controlled in a similar fashion, using an alpha level of 0.0277.

The overall family-wise error rate is controlled at alpha level of 0.05, and accounts for the interim and final analyses for the primary and secondary endpoints.

10.5.4.2. Primary Efficacy Endpoint Analysis

The primary objective of the study is to compare the proportion of patients with effective hemostasis (excellent or good as adjudicated by the blinded EAC) between andexanet and usual care. The following hypothesis will be evaluated:

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

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

Analysis will be performed using a Cochran-Mantel Haenszel (CMH) test stratified by time from symptom onset to baseline imaging scan (< 180 minutes vs. ≥ 180 minutes). The corresponding 95% confidence intervals (CIs) for the difference in proportions, and the proportions from the two groups, will be provided.

The study will be considered to meet its primary efficacy objective if the proportion of andexanet-treated patients with effective hemostasis (excellent or good as adjudicated by the independent EAC) is significantly higher ($p < 0.031$ at the interim analysis, OR $p<0.0277$ at the final analysis) than the proportion of patients with effective hemostasis randomized to usual care.

A sensitivity analysis will be performed using a CMH test stratified by intended-usual-care-agent and time from symptom onset to baseline imaging scan.

Further details of the primary analysis will be provided in the SAP.

10.5.4.3. Secondary Efficacy Endpoint Analysis

Anti-fXa Activity

The secondary objective of this study is to evaluate the effect of andexanet versus usual care on anti-fXa activity. The change, percent change in anti-fXa activity from baseline (most recent measurement prior to randomization) through the 2-hour time-point, and the minimum anti-fXa activity post-randomization (i.e., the nadir) will be summarized.

The secondary endpoint is the percent change in anti-fXa activity from baseline to nadir during the first 2 hours post-randomization. The analysis of this endpoint will be an Analysis of Covariance (ANCOVA) on the ranked data, including time from symptom onset to baseline imaging scan (< 180 minutes vs. ≥ 180 minutes), and baseline anti-fXa activity as covariates.

10.5.4.4. Additional Efficacy Analyses

Thrombin generation parameters (with ETP as the primary measure) will be obtained at baseline, 1 hour, and 12 hours post-randomization. The difference between the two treatment groups will be evaluated using a mixed effects model similar to the model described below for the analysis of the NIHSS and GCS scores.

The change from baseline in NIHSS and change from baseline in GCS will be analyzed using a mixed linear model with covariates, including the baseline measurement and the following fixed effect terms:

- Stratification factor of time from symptom onset to baseline imaging scan (< 180 minutes vs. ≥ 180 minutes)
- Treatment arm (usual care/andexanet)
- Time (measurements at 2, 3, 6, 12, 24, and 72 hours post-randomization)
- Treatment-by-time interaction

Patients will be treated as a random effect to take account of the correlation of the measurements within the same patient.

Neurologic deterioration at 24 hours defines deterioration as meeting at least one of the following 2 criteria:

- An increase in NIHSS score ≥ 4 at 24 hours post-randomization compared with baseline;
- A decrease in GCS score ≥ 2 at 24 hours post-randomization compared with baseline.

The CMH test stratified by time from symptom onset to baseline imaging scan will be used to test the treatment difference in the proportion of neurologic deterioration at 24 hours.

Change from baseline in mRS scores at 30 days post-randomization will be analyzed using a proportional odds model adjusted for baseline mRS, the stratification factor, treatment arm, and potentially other clinical factors.

The relationship between anti-fXa activity and the achievement of clinical events such as hemostatic efficacy and mortality will be evaluated. A logistic regression adjusted for potentially other clinical factors, the stratification factor in the primary efficacy analysis, and treatment arm will be used to evaluate the relationship.

Further details of these analyses will be provided in the SAP.

10.6. Safety Endpoints and Summaries

The following safety endpoints will be evaluated:

- Occurrence of TEs, confirmed by adjudication, through 30 days post-randomization.
- In-hospital mortality (during index hospitalization; all-cause, cardiovascular [CV], and bleeding).
- 30-day all-cause, CV, and bleeding mortality (the latter defined as death within 72 hours of randomization, not due to a TE).
- Proportion of patients with invasive intracranial procedures performed post-randomization to manage the intracranial hematoma and/or its complications.
- Length of initial hospitalization for primary bleeding event.
- Total time admitted to the intensive care unit during the initial hospitalization.
- Proportion of re-hospitalizations, including total number of re-hospitalizations and total days re-hospitalized, at 30 days post-randomization.
- AEs and vital signs.
- Antibodies to FX, FXa, and andexanet.
- Neutralizing antibodies to FX, FXa, and andexanet.

Safety will be assessed by examination of AEs (including central adjudication of TEs), survival status (including central adjudication of deaths), occurrence of invasive procedures, hospitalization data, laboratory parameters (i.e., antibody testing), and vital signs. Only clinically significant changes will be reported as AEs (see Section 8.1).

10.6.1. Adverse Events

Treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred terms as defined by the Medical Dictionary for Regulatory Activities (MedDRA) with the version in effect at the time of analysis.

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 a study-related procedure; 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 World Health Organization (WHO) Drug Dictionary (DD).

10.6.2. Thrombotic Events

All potential TEs up to the Day 30 visit will be assessed by the EAC and summarized descriptively. 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. In addition to Investigator reporting, ongoing periodic review of AEs to identify potential TEs to be submitted for adjudication will be conducted by the Sponsor. Detailed definitions of TEs assessed by EAC (including arterial systemic embolism, DVT, MI, PE, stroke, and TIA) will be provided in the Adjudication Charter as well as in Appendix K.

10.6.3. Deaths

All deaths will be assessed by the blinded EAC. Deaths will be summarized by all cause, death adjudicated as due to CV or non-CV causes, and death due to bleeding. In hospital deaths and 30-day mortality by all cause will be also summarized.

Thirty-day mortality will be analyzed using a Cox proportional hazards model (for survival), with analyses adjusted for the stratification factor as in the primary efficacy analysis treatment arm, and potentially other clinical factors. Details will be provided in the SAP.

10.6.4. Invasive Procedures

The number of patients with invasive intracranial procedures performed post-randomization will be summarized descriptively. All surgeries and interventional procedures specifically intended to manage the hematoma and/or its complications will be counted, including Burr holes, craniotomies, and placement of intraventricular catheters.

10.6.5. Hospitalizations

The length of initial hospitalization for primary bleeding event, the total time spent in the intensive care unit in the initial hospitalization, and the occurrence of re-hospitalizations (including total number of re-hospitalizations and total days re-hospitalized) up to 30 days post-randomization will be summarized descriptively.

10.6.6. Laboratory Parameters

The results of antibody assays including those for FX, FXa, and andexanet, and results for other safety laboratory parameters, will be summarized by time-point. Neutralizing antibodies for the above epitopes will be summarized by time-point as appropriate.

10.6.7. Vital Signs

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

10.7. Interim Analyses

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

10.7.1. Stopping Criterion Due to Efficacy at Interim

The overall type I error for the interim and final analysis is controlled at 5% by employing the alpha spending function by Lan and DeMets based on Pocock boundaries [6]. If the interim p-value < 0.0310 for comparing andexanet and usual care in the primary endpoint analysis, DSMB may recommend stopping the study. In this case, the efficacy results from the interim analysis (with 50% of the anticipated participants) will be used for regulatory communication and submission. Enrollment of patients will proceed without interruption while the analysis is ongoing, resulting in more than 50% of the anticipated participant in the final data cutoff; efficacy analysis on the final data cutoff will be considered as supportive.

10.7.2. Sample Size Re-estimation at Interim

If the DSMB recommendation at interim is to continue the study, a pre-planned sample size re-estimation (SSR) will be performed by the DSMB-associated statistician with the interim data. The SSR will be based on a conditional power (CP) of comparing andexanet and usual care at final (n=900) given the interim data, using a promising zone between 30% and 90% [31]. The assumption used for CP calculation is that the rate of hemostatic efficacy in andexanet and usual care at final is 80% and 70%, respectively. Based on the observed CP, DSMB will recommend:

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

10.7.3. Primary Analysis if Study is Continued from Interim

When no change in sample size occurs (i.e., interim decision to keep the original planned sample size), the conventional Cochran–Mantel–Haenszel (CMH) statistics will be used at final to determine statistical significance [1].

In contrast, if the total sample size is increased per interim analysis decision, then the final analysis will use the weighted statistic proposed by Cui, Hung, and Wang (2004) [32].

In this case, the test statistic at final is a weighted sum of the test statistic at interim (stage 1, $n_1 = 450$), and the test statistics based on additional participants (stage 2, $n_2 = 750$); the weight is 0.5 to avoid introducing bias. The weighted statistics is calculated as below

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

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

10.8. Subgroup Analyses

Subgroup analyses may include, but not necessary be limited to, the following parameters: baseline anti-fXa activity above and below 30 ng/mL, baseline anti-fXa activity above and below 75 ng/mL, age (less than 65, 65-74, 75 or greater), sex, race (all groups with 5 or more patients), geographical region (North America, Europe, Asia), FXa inhibitor at randomization, indication for FXa inhibitor (atrial fibrillation, VTE, other), time at randomization since last FXa inhibitor dose (within 8 hours or more than 8 hours), andexanet dose, hematoma expansion risk as measured by baseline hematoma volume (< 30 mL, ≥ 30 mL; < 0.5 mL, ≥ 0.5 mL), determination of ICrH score at baseline(< 3, ≥ 3), baseline intracranial bleed location, and usual care received (andexanet vs PCC, andexanet vs non-PCC).

11.0 STUDY COMMITTEES AND COMMUNICATIONS

Charters have been established accordingly for the committees. In brief, the purpose of each committee is as follows:

- **Independent EAC:** The EAC will oversee the adjudication of hemostatic efficacy within the first 12 hours post-randomization. Additionally, all TEs and deaths will be adjudicated. The EAC will remain blinded to treatment assignment for all patients.
- **Independent DSMB:** Monitor all safety and efficacy data. Evaluate interim analysis performed by the independent statistician and make recommendations for study modification or stopping due to efficacy or safety reasons.
- **Steering Committee:** Overall governance and oversight of the study; assessment and management of country-specific or region-specific issues and activities.
- **Executive Committee:** Oversight of general study conduct and ad hoc issues as they arise

12.0 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

12.1. Institutional Review Board or Independent Ethics Committee

This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulations.

The protocol, substantial protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator/Sponsor and reviewed and approved by the IRB/IEC before the study is initiated. If any of these documents require regulatory/health authority approval per local regulations, the Sponsor will also obtain such approval before the study is initiated. Any substantial amendments to the protocol will require IRB/IEC and, per local regulations, regulatory/health authority approval before implementation of changes made to the study design except for changes necessary to eliminate an immediate hazard to study participants. The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Directive 2001/20/EC, EU Clinical Trial Regulation (No. 536/2014) (if applicable), and all other applicable local regulations.

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

12.2. Informed Consent

It is the responsibility of the Investigator or designee to obtain signed (written or electronic signature) informed consent (and assent, where applicable) from all study participants or the participant's LAR prior to performing any study-related procedures, including screening assessments.

The Investigator or designee will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her LAR, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their LAR will be required to sign a statement of informed consent (or assent) or a certified translation, if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The participant's medical record must include a statement that signed (written or electronic) informed consent (or assent) was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent (or assent) must also sign the informed consent (or assent) form(s).

Participants or their LAR must be re-consented (or re-assented) to the most current version of the informed consent (or assent) form(s) during their participation in the study, as applicable.

A copy of the signed (written or electronic) informed consent (or assent) documentation (i.e., a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's LAR, as applicable. This document may require translation into the local language. Original signed (written or electronic) consent (or assent) forms must remain in each participant's study file and must be available for verification at any time.

Because of the critical nature of the illness under study and the possibility that patients will be unable to provide their own consent, proxy consents (defined as consent from an LAR) and/or emergency consents (defined as consent from a qualified medical professional) are allowed if permissible by local or regional laws and regulations.

12.3. Supplementary Documentation

Before initiation of the study, the Investigator must provide the Sponsor with the following documents (copies of which must be maintained by the Investigator):

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

5. Completed financial disclosure form for the Investigator and any sub-investigators listed on the Form FDA 1572. Investigators and sub-investigators will provide sufficient and accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after study completion.

12.4. Data Collection and Management Responsibilities

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

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

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

12.5. Study Records Retention

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

12.6. Deviation from the Protocol

The Investigator will not deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard, and then notify

the Sponsor's Medical Monitor and the IRB or IEC immediately regarding the type of emergency and course of action taken. Any action in this regard will be recorded on the appropriate CRF. Deviations due to non-compliance that render patient non-evaluable for key endpoints will be considered important deviations. Any other changes or deviations in the protocol will be made as an amendment to the protocol and must be approved by the Sponsor and the IRB or IEC before the changes or deviations are implemented. The Sponsor will not assume any responsibility or liability for any deviation or change that is not described as part of an amendment to the protocol.

12.7. Disclosure of Data

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

12.8. Drug Accountability

The Investigator must maintain accurate records of the amounts and dates andexanet was received from the Sponsor and prepared for the study, including the volume and concentration of stock solution prepared and remaining stock solution volume after dose preparation. All drug supplies must be accounted for at the termination of the study and a written explanation provided for any discrepancies. All partially used or unused drug supplies will be destroyed at the site, in accordance with approved written procedures, or returned to the Sponsor after written authorization is obtained from the Sponsor's Clinical Development department. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to the Sponsor. All records will be retained as noted in Section 12.5.

12.9. Study Monitoring

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Remote source data verification may be employed where permitted by local regulations. The scope of the source data verification is described in detail in the Clinical Monitoring Plan.

The Investigator/institution will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents. The IRB/IEC and

representatives of the Sponsor will be allowed 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 patient eligibility (e.g., medical history, concomitant medications) should be made available to the study monitor and to the IRB/IEC. The monitoring visits provide the Sponsor and the IRB/IEC with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of CRFs; assure that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records.

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APPENDIX A. SCHEDULE OF ACTIVITIES

	Screening & Baseline		Randomization	Treatment						Follow-Up					
STUDY DAY:	1									2	3		7 [16]	14 [16]	30 [17] or ET
TIME-POINT AND WINDOW: All time-points relative to randomization	-2 hours to -1 min	-15 min to -1 min	0	Within 30 min	1 hour ± 15 min	2 hours ± 15 min	3 hours ± 15 min	6 hours ± 30 min	12 hours ± 1 hour	24 hours ± 2 hours	48 hours ± 3 hours	72 hours ± 4 hours	+ 3 days	+ 6 days	+ 7 days
Obtain Consent [1]	X														
Determine Eligibility	X														
Obtain Medical History [2]	X														
Obtain Prior Medications [2]	X														
Vital Signs (SBP, DBP, HR, RR, temp)	X				X	X		X	X	X	X	X			X [18]
Height and weight [3]	X														
Central Lab: Anti-fXa Activity[4]		X			X	X									
Central Lab: Thrombin generation	X				X				X						
Central Lab: Antibodies to FX, FXa, andexanet; neutralizing antibodies to FX, FXa, andexanet	X														X [19]
Central Lab: TFPI Activity[22]		X			X	X			X						X
Local Lab: Pregnancy Test [5]	X														
Local Labs: Haematology, Coagulation, and Serum Chemistry (performed per local practice)	X								X						X [18]

	Screening & Baseline		**Randomization**	**Treatment**						**Follow-Up**					
STUDY DAY:	**1**									**2**	**3**		**7** [16]	**14** [16]	**30** [17] **or ET**
TIME-POINT AND WINDOW: All time-points relative to randomization	**-2 hours to -1 min**	**-15 min to -1 min**	**0**	**Within 30 min**	**1 hour ± 15 min**	**2 hours ± 15 min**	**3 hours ± 15 min**	**6 hours ± 30 min**	**12 hours ± 1 hour**	**24 hours ± 2 hours**	**48 hours ± 3 hours**	**72 hours ± 4 hours**	**+ 3 days**	**+ 6 days**	**+ 7 days**
Head CT or MRI [6]	X								X (11-15 hrs allowable)						
NIH Stroke Scale Score	X					X	X	X	X[14]	X[14]		X			
Glasgow Coma Scale Score	X					X	X	X	X[14]	X[14]		X			
Modified Rankin Scale Score	X [15]														X
EQ-5D															X
Randomization			**X**												
Andexanet arm: Administer andexanet bolus immediately followed by an infusion [7]				**Bolus + Infusion** Initiate no later than 30 min after randomization, and preferably within 2 hours of the baseline brain imaging scan.[20]											
Usual Care arm: Administer usual care [8]				X											
Record Blood Products & Hemostatic Treatments [9]				X						X	X	X	X	X	X
Record Intracerebral hemorrhage-related Diagnostic & Therapeutic Procedures [10]				X						X	X	X	X	X	X

	Screening & Baseline		Randomization	Treatment						Follow-Up					
STUDY DAY:	1									2	3		7 [16]	14 [16]	30 [17] or ET
TIME-POINT AND WINDOW: All time-points relative to randomization	-2 hours to -1 min	-15 min to -1 min	0	Within 30 min	1 hour ± 15 min	2 hours ± 15 min	3 hours ± 15 min	6 hours ± 30 min	12 hours ± 1 hour	24 hours ± 2 hours	48 hours ± 3 hours	72 hours ± 4 hours	+ 3 days	+ 6 days	+ 7 days
Record Hours in ED, ICU/Critical Care, General Hospital Floor, and total as an Inpatient and document Rehospitalization [11]				X						X	X	X	X	X	X
Record Adverse Events [21]	X			X						X	X	X	X	X	X
Record Concomitant Medications [12]				X						X	X	X	X	X	X
Ascertain Survival Status				X						X	X	X	X	X	X
Blood Pressure Management[13]	X	X	X	X						X	X	X			

BP = blood pressure; CBC = complete blood count; CRF = case report form; CT = computed tomography; DBP = diastolic blood pressure; ED = emergency department; EQ-5D = EuroQol-5 Dimension; ET = Early Termination; FX = Factor X; FXa = Activated factor X; GCS = Glasgow Coma Scale; HR = heart rate; hrs = hours; ICU = intensive care unit; INR = international normalized ratio; IV = Intravenous; lab = laboratory; min = minute(s); MRI = magnetic resonance imaging; mRS = Modified Rankin Scale; NIH = National Institutes of Health; NIHSS = National Institutes of Health Stroke Scale; RR = respiratory rate; SAE = serious adverse event; SBP = systolic blood pressure; TE = thrombotic event; temp = temperature

[1] Unless exception for informed consent for emergency procedures has been obtained and only in accordance with local laws and regulations.

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

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

[4] Samples for anti-fXa activity should be drawn at three time-points; one at baseline and at 1- and 2-hours post-randomization.

[5] Pregnancy test in females of childbearing potential only; test may be done on urine or serum.

[6] Data from the head CT or MRI done to confirm the diagnosis or establish the extent of intracerebral hemorrhage will be recorded as the baseline time-point and must occur within 2 hours prior to randomization. A repeat baseline CT or MRI prior to randomization is permitted.

[7] For patients randomized to andexanet, andexanet will be given via an IV bolus administered over ~15 to 30 minutes followed immediately by a continuous infusion administered over ~120 minutes.

[8] For patients randomized to usual care, Investigators may initiate, within 3 hours of randomization any available therapy (including no treatment) other than andexanet to control bleeding and manage their patient during the 12-hour post-randomization period. Treatment duration will depend on usual care used.

[9] Record blood products and hemostatic treatments used specifically for treatment of intracerebral hemorrhage.

[10] Record procedures performed to evaluate bleeding source/extent and for treatment of intracerebral hemorrhage. This should include CT or MRI scans.

[11] Record through initial hospital discharge and rehospitalization (as applicable).

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

[13] To minimize the effects of blood pressure on hematoma expansion, Investigators should consider maintaining SBP at a target of 140 mmHg as medically warranted in both treatment arms.

[14] The 12-hour and 24-hour NIHSS and GCS assessments must be performed in a blinded manner.

[15] The mRS should reflect the patient's neurological status prior to acute illness (pre-morbid).

[16] The Day 7 and Day 14 visits may be conducted by phone.

[17] Window: Days 30-37. Patients who discontinue from the study before this visit should undergo an Early Termination visit.

[18] To be performed at Early Termination only if these assessments have not yet been performed at any point during treatment.

[19] Patients with a positive anti-andexanet antibody response at the Day 30 visit should return for a follow up anti-andexanet antibody test within 30 days of when the positive test is communicated to the Investigator, or approximately 120 days post-randomization, whichever is later. Only patients with a positive Day 30 anti-andexanet antibody test result are required to return for this visit. Adverse events, concomitant medications and survival status will also be collected.

[20] To accommodate dosing within 2 hours of the baseline scan closest to randomization, reconstitution of andexanet prior to randomization will be allowed.

[21] Adverse events including SAEs and TEs, and survival will be followed through the Day 30 post-treatment visit for all patients.

[22] TFPI activity measurements will be included for plasma samples collected for anti-fXa activity (baseline [-15min to -1min], 1h, and 2h), thrombin generation (12h) and neutralizing antibodies FX/FXa (30d).

APPENDIX B. ADJUDICATION CRITERIA FOR HEMOSTATIC EFFICACY

Excellent (effective)	• Change from baseline in NIHSS of +6 or less at the 12-hour time-point, AND the following imaging criteria: • ≤ 20% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at the 12-hour time-point. • No rescue therapies[a] administered between 3 hours and 12 hours after randomization.
Good (effective)	• Change from baseline in NIHSS of +6 or less at the 12-hour time-point, AND the following imaging criteria: • > 20% but ≤ 35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan at any time between the completion of initial randomized treatment and the 12-hour time-point. • No rescue therapies[a] administered between 3 hours and 12 hours after randomization.
Poor/None (not effective)	• If a patient meets any one of the following criteria, they are considered to have poor/none hemostatic efficacy: • Change from baseline in NIHSS of +7 or more at the 12-hour time-point. • >35% increase in hematoma volume compared to baseline on a repeat CT or MRI scan performed at any time between the completion of initial randomized treatment and the 12-hour time-point. • Any initiation of rescue therapies greater than 3 hours after randomization and up to 12 hours post-randomization should result in poor/none hemostatic efficacy. • Any administration of andexanet starting greater than 3 hours after randomization and up to 12 hours post-randomization should result in poor/none hemostatic efficacy. • Any surgical procedures specifically intended to treat the hematoma occurring between 3 hours after randomization and up to 12 hours post-randomization should result in poor/none hemostatic efficacy.
Not Evaluable	• Insufficient information available to determine change from baseline in NIHSS, OR • Insufficient imaging information (i.e., missing or uninterpretable imaging scan) to determine change from baseline in volume, OR • Insufficient information available to determine whether patient received rescue therapy. • These cases will be further adjudicated to determine if they are non-evaluable from administrative reasons (e.g., scan not available for technical reason, transfer to another facility, or hematoma drainage not due to clinical deterioration) or clinical reasons (scan not available because of patient deterioration). Cases assessed as non-evaluable for clinical reasons will be imputed as having poor/none hemostatic efficacy.

Note: This Appendix is intended only as a guide to Investigators and is not intended to be comprehensive. Full details on the rating of hemostatic efficacy are provided in the Adjudication Charter.

[a] Rescue therapies defined as any pro-coagulant replacement factor products (e.g., 3- and 4-factor prothrombin complex concentrates, activated PCCs, FEIBA®, recombinant fVIIa, plasma, FFP, whole blood), any systemic or local hemostatic therapies (except tranexamic acid), or the conduct of unplanned surgeries/procedures to treat the hematoma.

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 SCALE (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. NATIONAL INSTITUTES OF HEALTH STROKE SCALE

N I H 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.	_____

Rev 10/1/2003

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**	_____

Rev 10/1/2003

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:_____	_____

Rev 10/1/2003

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-_

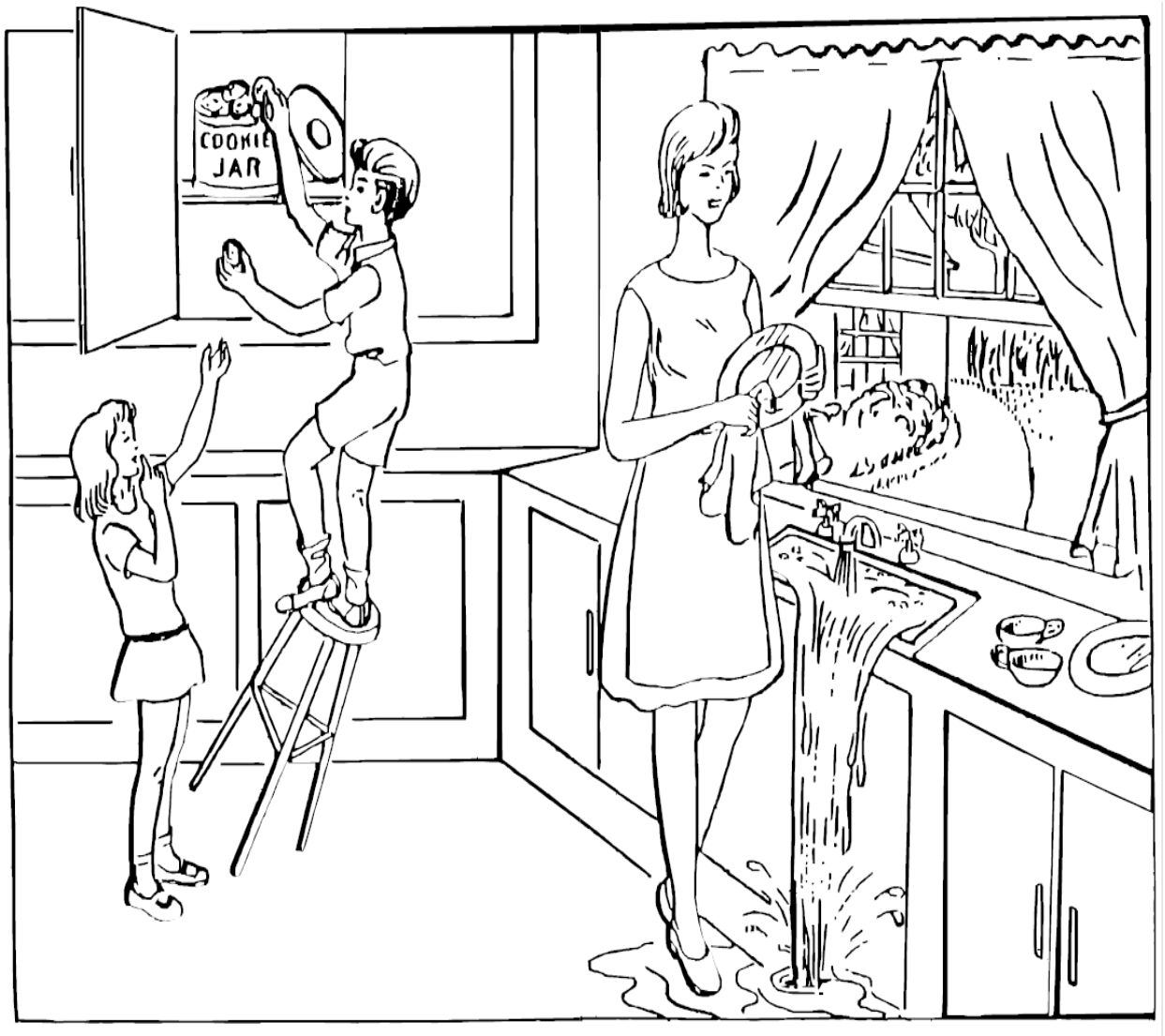
Pt. Date of Birth ___ ___/___ _

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.


COOKIE
JAR

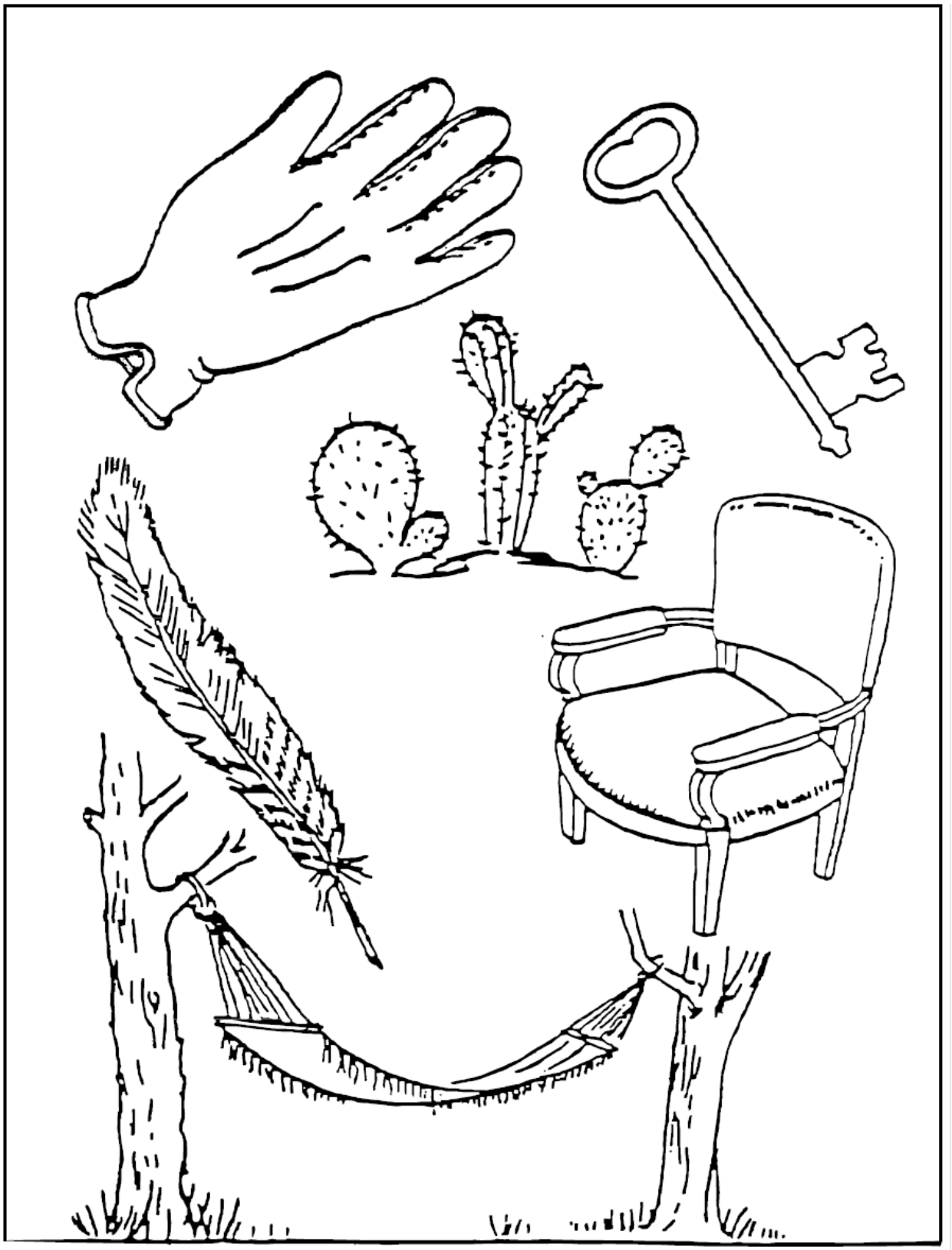
You know how.

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 F. COVID-19: POTENTIAL RISKS AND MITIGATION MEASURES

Risk Category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potentially higher risk population for SARS-CoV-2 infection	It is unknown how this may impact their risk for SARS-CoV-2 infection.	During the time that the COVID-19 pandemic is active, Alexion will recommend that sites in a position to start the study and enroll participants follow national and institutional guidance regarding prevention of SARS-CoV-2 infection. Additionally, during that time period, it is expected that Investigators and their staff will take all possible precautions in order to minimize a participant's potential exposure to SARS-CoV-2 infection. Depending on the site, these precautions will consist of measures such as social distancing, temperature screening, enhanced cleaning, and use of personal protective equipment for participants, staff, and caregivers as necessary.
Healthcare institution availability for non-COVID-19-related activities	COVID-19 pandemic may impact the workload of healthcare institutions globally and may reduce staff availability to perform non-urgent activities and non-COVID-19 related activities.	During the time that the COVID-19 pandemic is active, Alexion will not open study sites or enroll new participants at sites unless the sites have the resourcing and capabilities to implement the study per protocol.
Data quality and integrity	Lack of availability of site personnel to perform study assessments and capture study specific data in a timely manner and to maintain adequate quality standards. Lack of availability of site personnel to ensure adequate and continuous chain of custody, storage conditions, and monitoring for investigational product and biological samples. Inability of study monitors and quality personnel to conduct in-person visits to exercise adequate oversight of study execution at investigational sites. Missing data (COVID-19 pandemic may impact study visit schedules and increase missed visits and/or participant study discontinuations inadvertently resulting in missing data [e.g., for protocol-specified procedures]).	During the time that the COVID-19 pandemic is active, Alexion will only open study sites that report enough personnel capacity to sufficiently conduct clinical study-related activities. During this timeframe, participants eligibility as well as site capacity will be reviewed by the site Investigator and the study Medical Monitor prior to Screening. Each site is also evaluated for the capacity to perform remote monitoring visits and remote source data verification. During the time that the COVID-19 pandemic is active, it will be important to capture specific information in the eCRF that explains the reason the data is missing (e.g., missed study visits or participant study discontinuations due to COVID-19).

COVID-19 = coronavirus disease 2019; eCRF =electronic case report form; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

APPENDIX G. EXAMPLES OF PLANNED MINIMALLY INVASIVE SURGERIES/ PROCEDURES ALLOWED

- Neurologic interventions (e.g., Burr hole, craniotomy) that are specifically indicated for a reason other than hematoma evacuation (e.g., intracranial pressure monitoring). Any procedure intended to drain a hematoma, or potentially having an effect on hematoma volume, is excluded.
- Joint arthroscopy
- Thoracentesis
- Pericardial puncture/drainage
- Embolization
- Endoscopy with cauterization/embolization
- Cystoscopy
- Laparocentesis
- Lumbar puncture
- Colonoscopy
- CT-guided abscess drainage
- Joint arthrocentesis
- Percutaneous biopsy

APPENDIX H. DISSEMINATED INTRAVASCULAR COAGULATION SCORING ALGORITHM

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

Source: Levi 2009 [33].

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

APPENDIX I. DEFINITIONS OF CARDIOGENIC SHOCK, SEVERE SEPSIS AND SEPTIC SHOCK

Cardiogenic shock is a cardiac disorder that results in both clinical and biochemical evidence of tissue hypoperfusion [34]. The definition of cardiogenic shock may be clinically determined and consists of the following: SBP < 90 mmHg for at least 30 minutes, OR

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

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

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

Severe sepsis is defined as sepsis plus sepsis-induced tissue hypoperfusion or organ dysfunction with any of the following thought to be due to the infection:

- Sepsis-induced hypotension
- Lactate above ULN
- Urine output < 0.5 mL/kg/h for more than two hours despite adequate fluid resuscitation
- Acute lung injury with arterial oxygen partial pressure/fractional inspired oxygen PaO_2/FIO_2 < 250 mm Hg in the absence of pneumonia as infection source
- Acute lung injury with PaO_2/FIO_2 < 200 mm Hg in the presence of pneumonia as infection source
- Creatinine > 2 mg/dL (176.8 µmol/L)
- Bilirubin > 4 mg/dL (34.2 µmol/L)
- Platelet count < 100,000/µL
- Coagulopathy (INR > 1.5)

Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria.

Sepsis-induced hypotension is defined as an SBP < 90 mm Hg, or mean arterial pressure < 70 mmHg, or a SBP decrease > 40 mm Hg, 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 [35].

APPENDIX J. DEFINITION OF FEMALE OF CHILDBEARING POTENTIAL

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

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

1. The patient has been post-menopausal (amenorrheic) for at least 1 year
2. The patient had a surgical bilateral oophorectomy (with or without hysterectomy) more than 6 weeks prior to screening
3. The patient had a hysterectomy
4. The patient is ≥ 65 years of age

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

Adjudication criteria for the diagnosis of TIAs, strokes, MIs, VTE, and arterial systemic embolism are provided below.

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

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

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

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

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

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

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

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

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

VTE is defined as a symptomatic DVT or PE confirmed by objective testing. Criteria for the objective confirmation of DVT include:

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

Criteria for the objective confirmation of PE include:

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

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

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

APPENDIX L. EUROQOL-5 DIMENSION (EQ-5D) QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐