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Statistical Analysis Plan: Part 2

A Phase 2 Randomized, Double-Blinded, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Andexanet Alfa Administered to Healthy Japanese and Caucasian Subjects

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STATISTICAL ANALYSIS PLAN: PART 2

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LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATA	Anti-test article antibodies
AT-III	Antithrombin-III
AUC	Area under the curve
BID	Twice a day
BLQ	Below Limit of Quantification
BP	Blood pressure
β-TG	Beta thromboglobulin
BUN	Blood urea nitrogen
CBC	Complete blood count
CL	Clearance
$C_{max/min}$	Maximum/minimum observed concentration
Cr	Creatinine
CRF	Case report form
CRO	Contract research organization
DVT	Deep venous thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
e-CRF	Electronic case report form
EOB	End of Bolus
EOI	End of Infusion
F1+2	Prothrombin fragment 1+2
FDA	(US) Food and Drug Administration
Fg	Fibrinogen
FSH	Follicle-stimulating hormone
FX	Factor X
fXa	Factor Xa
GCP	Good Clinical Practice
HR	Heart rate
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
ICF	Informed Consent Form
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
LOQ	Limit of Quantification
λ_z	Terminal or elimination rate constant
MI	Myocardial infarction
Min	Minute
mL	Milliliter
Ng	Nanogram
PD	Pharmacodynamic
PK	Pharmacokinetic
PI	Principal Investigator
PO	Orally
PT	Prothrombin time
Q	Every
QD	Once daily
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SC	Subcutaneous
SD	Standard deviation
$t_{½}$	Half-life
TAT	Thrombin-antithrombin complex
TFPI	Tissue factor pathway inhibitor
TEAE	Treatment emergent adverse event
t_{max}	Time to maximum observed concentration
ULN	Upper limit of normal
US	United States
VS	Vital signs
V_{ss}	Volume at steady state
VTE	Venous thromboembolism
WBC	White blood cells

1.0 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to prospectively outline in detail the data derivations, statistical methods and presentations of data in Study 16-508 so that valid conclusions can be reached to address the study objectives outlined in the protocol (Part 2). This SAP addresses only the Part 2 objectives of the study. A separate SAP was developed for Part 1 and the outcomes will be reported in a Clinical Study Report.

The analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the andexanet alfa clinical development program. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

1.1. Responsibilities

WCCTG will perform the statistical analyses for all clinical data collected. WCCTG is responsible for production and quality control of all tables, figures and listings.

1.2. Timing of Analyses

There will be one final analysis after final data lock following completion of Part 2, as detailed in this SAP.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The objectives of this study in Parts 1 and 2 are to assess the following in healthy subjects dosed to steady state with direct oral FXa inhibitors (apixaban, rivaroxaban, and edoxaban):

Efficacy Objectives

Primary Efficacy Objective

- To compare andexanet and placebo with respect to reversal of each FXa inhibitor as measured by anti-fXa activity.

Secondary Efficacy Objectives

- To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by free fraction of the inhibitor.
- To assess andexanet and placebo with respect to reversal of each FXa inhibitor as measured by restoration of thrombin generation.
- To assess the pharmacodynamics of andexanet in Japanese subjects and Caucasian subjects, as measured by anti-fXa activity, free fraction of the FXa inhibitor (apixaban), and restoration of thrombin generation. [Note that this objective only applies to Part 1 of the study, and hence is not addressed in this SAP]

Safety Objective

- To evaluate the safety of andexanet in Japanese subjects.

Pharmacokinetics Objectives

- To evaluate the pharmacokinetics of andexanet in Japanese subjects.
- To compare the pharmacokinetics of andexanet in Japanese subjects to the pharmacokinetics of andexanet in Caucasian subjects. [Note that this objective only applies to Part 1 of the study, and hence is not addressed in this SAP]

2.2. Endpoints

2.2.1 Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in anti-FXa activity from baseline to the end of infusion (EOI) nadir. The EOI nadir is defined as the smallest value for anti-FXa activity of 110 minutes after the start of the andexanet infusion (approximately 10 minutes prior to the end of the continuous infusion), End of Infusion (-2 mins), and the 5-minute time point after the end of the continuous infusion.

Baseline is defined as the value observed for Day 6 pre-Andexanet treatment (i.e., 3 hours post last dose of apixaban for Cohorts 6; for Cohort 7, 1.5 hours post last dose of edoxaban; and for Cohorts 8, 9, and 10, 8 hours past the last doses of apixaban, rivaroxaban and edoxaban, respectively). The primary analysis will be performed by cohort.

Secondary Efficacy Endpoints

- The percent change from baseline in anti-FXa activity at its end of bolus (EOB) nadir, where the EOB nadir is defined as the smallest value for anti-fXa activity at the +2 minute or +5 minute time point after the completion of the andexanet bolus.

- The change and percent change from baseline in free FXa inhibitors concentration (ng/mL) at its EOB nadir, where EOB nadir is defined as the smallest value for free FXa inhibitors at the +2 minute or +5 minute time point after the completion of the andexanet bolus.

- The change and percent change from baseline in free FXa inhibitors concentration (ng/mL) at its EOI nadir, where EOI nadir is defined as the smallest value for free FXa inhibitors between 110 minutes after the start of the andexanet infusion and ending 5 minutes after the end of the andexanet infusion (inclusive).

- The change in thrombin generation from baseline to its EOB peak, where EOB peak is defined as the largest value for thrombin generation between the +2 minute time point and the +5 time point after the end of the andexanet bolus (inclusive).

- The percentage of cases with thrombin generation above the lower limit of the normal range at its EOB peak, between the +2 minute time point and the +5 time point after the end of the andexanet bolus (inclusive). The lower limit of normal range is defined as overall mean for thrombin generation prior to start of treatment (i.e., Day 1) minus the standard deviation.

- The change in thrombin generation from baseline to its EOI peak, where EOI peak is defined as the largest value for thrombin generation between 110 minutes after the start of the andexanet infusion and ending 5 minutes after the end of the andexanet infusion (inclusive).

- The percent of cases with thrombin generation above the lower limit of the normal range at its EOI peak, where EOI peak is defined as the largest value for thrombin generation between 110 minutes after the start of the andexanet infusion and ending 5 minutes after the end of the andexanet infusion. The lower limit of normal range is defined as Mean – 1SD of thrombin generation at Day 1 prior to start of treatment combined for all cohorts in Part 2.

Only subjects with both a baseline and a post-baseline assessment are to be included in within and between-cohort comparisons.

2.3. PK Parameters

Plasma samples for andexanet will be collected at multiple time points on Day 6 through Day 9. From these, following non-compartmental PK parameters based on the total administered andexanet dose will be computed: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\infty)}$, $t_{1/2}$, CL, V_{ss}, and λ_z.

Factor Xa inhibitors: Plasma concentrations of both unbound and total fXa inhibitors will be measured in this study. Plasma samples for fXa inhibitors (total and unbound) will be collected on Day 1 (pre-dose only), multiple time points (specified in Appendix A. Study Events Flow Chart) on Day 5 through Day 8 and once on Day 9 and Day 10.

The following non-compartmental PK parameters will be computed for total plasma apixaban, rivaroxaban, and edoxaban: C_{max}, C_{bolus} (end of bolus + 2 minutes), T_{max}, CL/F, $AUC_{(0\text{-last})}$, $AUC_{(0\text{-}\tau)}$, $t_{1/2}$, and λ_z. The plasma levels of the edoxaban metabolite D21-2393 will be reported in the bioanalytical report.

2.4. Safety Endpoints

The following safety parameters will be analyzed:

- Adverse events, physical exam, vital signs, oxygen saturation, ECG, clinical laboratory values Serial clinical assessments for venous thromboembolic events.

- Antibodies to andexanet, FX, FXa, and HCPs; neutralizing antibodies to andexanet, FX, and FXa (if antibodies are detected for the subject at any time point).

- Coagulation markers: F1+2, TAT, D-dimer

Exploratory Safety Endpoints

TFPI activity will be evaluated as an exploratory safety endpoint. This parameter was defined as an efficacy endpoint in the protocol, but it will be analyzed as a safety endpoint.

3.0 STUDY DESIGN

This is a single-center, randomized, double blind, and placebo-controlled trial designed to evaluate the efficacy, safety, and PK of andexanet in healthy Japanese subjects taking direct FXa inhibitors at therapeutic doses. Reversal of anticoagulation will be evaluated by measuring anti-fXa activity, unbound FXa inhibitor plasma levels, and thrombin generation.

A total of 10 cohorts will be studied in two parts. Part 1 consisted of 5 cohorts (i.e., Cohorts 1 – 5) and was discussed in the Statistical Analysis Plan for Part 1, version 1.0, dated July 29, 2018. Part 2 which is the focus of this SAP, consists of Cohorts 6-10 and will evaluate the efficacy (as assessed by anti-fXa activity reversal), safety, and PK of andexanet in Japanese subjects with various additional dosing scenario that were not evaluated in Part 1.

3.1 Study Treatments and Dose Administration

At least 57 subjects are enrolled in part 2 of this study (in Cohorts 6-10).

Table 1: Drug/Dosing Assignments for ALL Cohorts

Cohort	fXa Inhibitor	Andexanet	N(Active/Placebo)
Part 1			
1	Apixaban 5 mg BID	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Japanese 9 (6/3)
2	Rivaroxaban 15 mg BID	800 mg bolus+ 8 mg/min 120 minute infusion/placebo (andexanet dosing at 4 hours post-rivaroxaban)	Japanese 9 (6/3)
3	Edoxaban 60 mg QD	800 mg bolus+8 mg/min 120 minutes infusion /placebo (andexanet dosing at 3 hours post-edoxaban)	Japanese 12 (8/4)
4	Edoxaban 60 mg QD	800 mg bolus+8 mg/min 120 minute infusion/placebo (andexanet dosing at 90 minutes post-edoxaban)	Japanese 12 (8/4)
5	Apixaban 5 mg BID	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Caucasian 9 (6/3)

Part 2			
6	Apixaban 10 mg BID	800 mg bolus+8 mg/min 120 minute infusion/placebo (andexanet dosing at 3 hours post-apixaban)	Japanese 9 (6/3)
7	Edoxaban 30 mg QD	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 90 minutes post-edoxaban)	Japanese 12 (8/4)
8	Apixaban 10 mg BID	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post-apixaban)	Japanese 9 (6/3)
9	Rivaroxaban 15 mg BID	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post-rivaroxaban)	Japanese 15 (10/5)
10	Edoxaban 60 mg QD	400 mg bolus+4 mg/min 120 minute infusion/placebo (andexanet dosing at 8 hours post-edoxaban)	Japanese 12 (8/4)

3.2 Sample Size Justification

For all cohorts, subjects will be randomized in a 2:1 ratio of treatment with andexanet or placebo, respectively. If enrolled subjects discontinue early from the study or have missing data for any reason, the Sponsor may elect to add up to 3 additional subjects (with newly blinded treatment assignments) within the discontinued subject's assigned cohort.

Part 1

Apixaban 5 mg BID (Cohort 1 and Cohort 5)

The mean (SD) of the primary endpoint in Study 14-503 Part 2 which assessed the reversal of apixaban 5 mg BID anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -92.3% (SD = 2.8%) and -32.7% (SD = 5.6%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in anti-fXa activity in this study are assumed to be -90% (SD = 5%) and -35% (SD = 10%) for andexanet and placebo arms, respectively. The standard deviations in both arms are assumed larger than the observed values in the previous study to provide adequate power for the comparison. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test.

Rivaroxaban 15 mg BID (Cohort 2)

The mean (SD) of the primary endpoint in Study 14-504 Part 2 which assessed the reversal of rivaroxaban 20 mg QD anticoagulation with andexanet administered as an IV bolus followed by a 2-hour infusion were -96.7% (SD = 1.8%) and -44.8% (SD = 11.7%) for andexanet and placebo arms, respectively. Based on these results, the percent changes from baseline in antifXa activity are assumed to be -90% (SD = 5%) and -45% (SD = 15%) for andexanet and placebo arms, respectively. Under these assumptions, a total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

Edoxaban 60 mg QD (Cohort 3: andexanet dosing at 3 hours post-edoxaban)

In Cohort 2 of Study 12-502 Module 4 which assessed the reversal of edoxaban anticoagulation with andexanet, the mean (SD) of the percent change from baseline anti-fXa activity at the end of infusion was -70.28% (SD = 5.64%) for the andexanet arm. In Cohort 1 and Cohort 2 of the same study, the mean (SD) of the percent change from baseline at 2 hours after the end of bolus was -40.31% (SD = 12.25%) for placebo. Based on these results, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 6%) and -40% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test.

Edoxaban 60 mg QD (Cohort 4: andexanet dosing at 90 minutes post-edoxaban)

There are no actual data of andexanet administration at 90 minutes after edoxaban dosing. Based on the result predicted by the PK-PD model developed using the data of Study 12-502, the percent changes from baseline in anti-fXa activity for andexanet and placebo are assumed as -70% (SD = 15%) and -30% (SD = 15%), respectively. Under these assumptions, a total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test.

Part 2

Apixaban 10 mg BID (Cohort 6: andexanet dosing at 3 hours post apixaban)

A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %change from baseline in anti-fXa activity (%CHB in anti-fXa activity) at nadir around EOI were -97% (SD = 0.8%) and –36% (SD = 3.3%) for andexanet and placebo arms, respectively. In the power calculation, -95% (SD = 10%) and -40% (SD = 10%) are assumed.

Edoxaban 30 mg QD (Cohort 7: andexanet dosing at 90 min post edoxaban)

A total number of 12 subjects (8 active and 4 placebo) will provide approximately 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two sample exact Wilcoxon rank sum test. Given the dose proportionality, the underlying assumptions are supported by data from Cohort 4 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -71% (SD = 13.6%) and –34% (SD = 12.8%) for andexanet and placebo arms, respectively. In the power calculation, -70% (SD = 15%) and -35% (SD = 15%) are assumed.

Apixaban 10 mg BID (Cohort 8: andexanet dosing at 8 hours post apixaban)

A total number of 9 subjects (6 active and 3 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 8 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at 3.5 hours after EOI was -51% (SD = 9.5%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 91.6% was used as reference because there are no actual data. In the power calculation, -90% (SD = 10%) and -50% (SD = 10%) are assumed.

Rivaroxaban 15 mg BID (Cohort 9: andexanet dosing at 8 hours post rivaroxaban)

A total number of 15 subjects (10 active and 5 placebo) will provide approximately 87% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test. For placebo arm, the underlying assumptions are supported by data from Cohort 2 of the 16-508 study, which the mean (SD) of %CHB in anti-fXa activity at 1.5 hours after EOI was -56% (SD = 12.1%). For andexanet arm, the mean of %CHB in anti-fXa activity predicted by the PK-PD model that is 86.5% was used as reference because there are no actual data. In the power calculation, -85% (SD = 15%) and -55% (SD = 15%) are assumed.

Edoxaban 60 mg QD (Cohort 10: andexanet dosing at 8 hours post edoxaban)

A total number of 12 subjects (8 active and 4 placebo) will provide at least 90% power to detect the difference at a significance level of 0.05 (two-sided) using the two-sample exact Wilcoxon rank sum test. The underlying assumptions are supported by data from Cohort 11 of the 16-512 study, which the mean (SD) of %CHB in anti-fXa activity at nadir around EOI were -64% (SD = 9.0%) and –39% (SD = 6.0%) for andexanet and placebo arms, respectively. In the power calculation, -65% (SD = 10%) and -40% (SD = 10%) are assumed.

3.3 Estimated Duration of Subject Participation and Follow-up

For each individual subject, the study duration will be approximately 6–12 weeks, depending on the length of Screening. The study periods are as follows:

- Screening: Days -45 to -1
- Anticoagulant Dosing: Days 1 to 6 (only morning dose on Day 6 for apixaban, rivaroxaban, and edoxaban)
- Andexanet Dosing: Day 6
- Safety Follow-Up: Days 7 to 36 (+3)

Study subjects will be domiciled from Day -1 to Day 10, and then discharged from the inpatient facility on Day 10 to continue outpatient follow-up through Day 36 (+3).

4.0 ANALYSIS POPULATIONS

The results from this study will be presented using the following populations:

4.1. PK Analysis Population

The PK analysis population will consist of all subjects who received a complete dose of andexanet and have missing data for no more than 3 plasma concentration timepoints. For calculation of the primary PK parameter, $AUC_{(0-\infty)}$, a minimum of 3 time points after T_{max} with evaluable concentration data will be required.

4.2. Efficacy Analysis Population

The Efficacy Analysis Population will include all randomized subjects who received andexanet or placebo during the double-blind treatment period and had at least one evaluable post-baseline efficacy assessment as well as the required baseline sample assessment. Efficacy populations will be defined for each efficacy endpoint separately based on available data. For the efficacy analysis, subjects will be presented in the treatment group to which they were randomized. Subjects will be included in the efficacy analysis set on change or percent change from baseline if they have a baseline value and at least one measurement post-baseline for the time point under consideration.

4.3. Safety Analysis Population

The safety analysis population will include all enrolled subjects who received any amount of study drug (andexanet or placebo) treatment. All subjects in the safety population will be associated with the treatment actually received.

5.0 GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

5.1. Key Definitions

The Study Day is the day relative to the first date of administration of the fXa inhibitor (Day 1).

Unless otherwise specified, Baseline is the pre-study drug (andexanet/placebo) measurement on Day 6, or Day 5 data at the matched time point if the Day 6 data are not available.

The treatment period is defined as Days 1-6 for those subjects dosed with either andexanet or placebo.

5.2. Visit Windows and Time Points

There are no plans to derive visit windows, and visits will be used in the analyses as reported on the eCRF.

The time points selected in the eCRF for the PD analysis are exact time points. However, for analysis purposes, the time point windows may be used for assigning the actual time points to the scheduled nominal time points.

5.3. Multiplicity Issues

For this early phase study, although andexanet and placebo are compared via a number of efficacy endpoints across a number of cohorts and time points, no multiplicity adjustment will be made to account for the potential inflation of the type 1 error rate.

5.4. Subgroup Analyses

Due to the small size of this study, no inferential subgroup analyses are planned.

5.5. Missing Data

For the PK evaluation, plasma concentration values for sample data points with missing data occurring prior to the last quantifiable data point, which will be assumed to be the point of clearance, will be interpolated.

In calculation of the concentration summaries and PK parameters, Below the Limit of Quantification (BLQ) values will be treated as follows:

- BLQ values in samples drawn prior to administration of study drug will be set to zero.
- Post-dose BLQ values in samples drawn prior to the first measurable concentration will be set to half the lower limit of quantitation (LLOQ).
- BLQ values that occur between two measurable concentration values will be treated as missing and excluded from the PK parameter calculation
- BLQ values that occur at the end of the concentration-time profile will be imputed to zero

In calculation of PD summaries, BLQ values will be set to LLOQ/2. For values above the limit of quantitation (ALQ), the values will be set to the upper limit of quantification.

In listings, BLQ values will be presented as "BLQ". The ALQ values will be presented as >ALQ. For calculation of the geometric mean, values below 1, the log value will be set as zero. Data may be excluded from the descriptive or inferential analyses if the result is based on unscheduled visits. In this case data will be presented in data listings with a flag for exclusion.

For the efficacy evaluation, primary comparison requires data for both pre-andexanet/placebo (i.e., baseline) and post-andexanet/placebo nadir or peak.

Baseline is defined as the value observed for Day 6 pre-Andexanet treatment (i.e., 3 hours post last dose of apixaban for Cohort 6; 1.5 hours post last dose of edoxaban for Cohort 7; and 8 hours post the last doses of apixaban, rivaroxaban and edoxaban for Cohorts 8, 9, and 10, respectively). The primary analysis will be performed by cohort. If data at the Day 6 baseline is missing, the Day 5 data at the matched time point will be used (i.e. if Day 6 pre-andexanet baseline is at 8 hours post the last dose of the inhibitor, the Day 5 time point should also be at 8 hours after dosing the inhibitor). If both the Day 6 and Day 5 measurements are missing, the baseline value will be considered as missing. For nadir or peak for the primary efficacy analysis, missing values will not be imputed. If baseline data and/or nadir is missing, the subject will be considered non-evaluable and excluded from the primary comparison.

As a sensitivity analysis, if both the baseline values on Day 6 and Day 5 are missing (as described above), the change and percent changed will be imputed to zero. If the post bolus value is missing, the missing value will be imputed with the nadir value observed prior to the 110 minutes after start of infusion. If the value for the infusion is missing, the missing value will be replaced with the nadir value for post EOI. If all values are missing for Bolus and infusion, change and percent change will be imputed to zero.

For prior and concomitant medication summaries, if the medication start date is completely missing then the medication will be considered to be both prior and concomitant unless it can be determined that the medication end date occurred prior to andexanet administration. If the medication start date is partially missing and the partial date is not sufficient to determine if the medication was taken after andexanet administration then the medication will be considered to be both prior and concomitant for the study unless the partial date is clearly after the date of andexanet administration (in which case it will be considered concomitant only) or the medication end date is prior to andexanet administration (in which case it is prior only).

For reporting AEs, the start dates and start times are important for the:

- Treatment emergent adverse event (TEAE) algorithm.
- Designation of unique AE occurrences.

- Designation of relatedness to study drug.

Completely missing or partially missing adverse event onset dates/times will be imputed as follows after due diligence to obtain accurate adverse event information has failed.

If the adverse event start date is completely missing, then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to administration of study medication. If this is the case, the adverse event will not be considered treatment emergent.

If the adverse event start date is partially missing and the partial date is not sufficient to determine if the event occurred after the administration of study medication, then the adverse event will be considered treatment emergent unless it can be determined that the adverse event end date occurred prior to the start of the study. In the unlikely event of a missing laboratory result, the result will be treated as missing for the laboratory abnormality summary.

6.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

6.1. Subject Disposition

Summary tables for subject disposition will be presented for all enrolled subjects (presented in table and listing summaries as All Subjects) by Cohort. The subject disposition summary will include subjects who received the FXa inhibitor, subjects randomized, subjects who received andexanet or placebo, subjects completing andexanet/placebo treatment, and subjects discontinued from the Study. In addition, disposition will be presented for the entire population grouped by andexanet and placebo. The primary reason for premature discontinuation from the study will be summarized for the Safety Population. A listing will be presented on subject disposition.

Summary statistics for FXa inhibitor doses will be presented by cohort. The number and percentage of subjects with interrupted or discontinued andexanet/placebo treatment will be reported by cohort.

6.2. Baseline and Demographic Characteristics

Baseline and demographic characteristics will be summarized for the safety population of part 2 of the study, using descriptive statistics such as frequencies, means, medians, standard deviations, minimums, and maximums. No inferential statistical analyses of these data are planned.

All Subjects in the Safety Population will be used to summarize the demographic and baseline characteristics with respect to height (cm), weight (kg), BMI (kg/m^2), sex, age (years) at entry into the study and race. Age will be calculated as:

[Date of Informed Consent – Date of Birth] / 365.25 rounded down to the nearest integer.

Age will be reported in years and summarized with descriptive statistics: n, arithmetic mean, standard deviation, median, range (i.e., minimum and maximum values). The number and percent of each sex will be presented using counts and percentages. Because all enrolled subjects will be of Japanese descent, race and ethnicity subgroups will not be specifically presented.

6.3. Medical History

Medical and surgical history and concomitant diseases will be coded according to version 21.1 of MedDRA. Frequency tables of the number and percentage of subjects by system organ class and preferred term will be provided for the Safety Population only.

6.4. Prior and Concomitant Medication

Medications will be separated into prior and concomitant medications. Prior medications are taken before the date of start of andexanet (or matching placebo). Concomitant medications are those taken from the start of andexanet or matching placebo through the end of the study.

Medications will be coded according to the most recent version of the WHO Drug Dictionary. Listings will present the Anatomical Therapeutic Chemical classification system (ATC) Class Level 2, Class Level 3, generic name, and the investigator term.

Prior medication and concomitant medication will be summarised for the Safety Population by Cohort from both parts. Frequency tables of the number and percentage of subjects by ATC Class Level 2 and ATC Class Level 3 will be provided.

6. 5. Protocol Deviations

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

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

Protocol deviations specific to the primary efficacy endpoint are as follows:

The percent change from baseline in anti-FXa activity to the EOI nadir will be defined by a specific evaluation period beginning 110 minutes after the start of the andexanet infusion and the 5- minute time point after the end of the continuous infusion (inclusive). Samples drawn outside these windows may be considered significant protocol deviations, especially if they impact the integrity of the data.

7.0 EFFICACY ANALYSES

7.1. Primary Efficacy Endpoint

Anti- FXa Activity at EOI

The primary efficacy endpoint is the percent change in anti-FXa activity from baseline to the nadir level. The nadir is defined as the smallest value for anti-FXa activity of 110 minutes after the start of the andexanet infusion (approximately 10 minutes prior to the end of the continuous infusion), end of infusion (-2 minute), and the 5-minute time point after the end of the continuous infusion. The primary analysis will be performed by cohort. Summary statistics will be provided for baseline, absolute value, change from baseline, and %change from baseline for each time point during evaluation period. Only subjects with both a baseline and a post-baseline assessment are to be included in within-cohort comparisons.

A two-sided Wilcoxon Rank Sum test will be used to compare the anti-FXa activity between andexanet and placebo at a significance level of 5%. Besides the p-value from the above test, the Hodges-Lehman estimate and 95% confidence interval will be derived for the difference in percent change from baseline between the treatments.

The above analyses will be based on the Efficacy Population.

7.2. Secondary Efficacy Endpoints

Anti- FXa Activity at EOB

Summary statistics similar to those provided for the EOI nadir analysis for anti-FXa activity will be provided for the EOB nadir endpoint where the EOB nadir is defined as the smallest value between the +2 minute and +5 minute timepoint after the end of the andexanet bolus. The summary statistics will be provided for baseline, absolute value, change from baseline, and %change from baseline for each time point during evaluation period. Only subjects with both a baseline and a post-baseline assessment are to be included in within-cohort comparisons.

Unbound (Free) Plasma Fraction of FXa Inhibitor at EOB and EOI

To characterize the difference in percent change in free FXa inhibitor concentration (ng/mL) from baseline to the EOB nadir level, where the EOB nadir is defined as the smallest value for free FXa inhibitors at the +2 minute or +5 minute time point after the completion of the andexanet bolus, a summary statistics for baseline, absolute value, change from baseline and %change from baseline will be provided at nadir and each time point during evaluation period. This analysis will be performed on all individual cohorts separately. A similar analysis will be performed for the EOI nadir defined as the smallest value between the 110 minute timepoint

after the start of the andexanet infusion and the 5-minute time point after the end of the continuous infusion.

Thrombin generation at EOB and EOI

The change in thrombin generation from baseline to its EOB peak, where the EOB peak is defined as the largest value for thrombin generation between the +2 minute time point and the +5 minute time point after the end of the andexanet bolus (inclusive), a summary statistics for baseline, absolute value, change from baseline will be provided at peak and each time point during evaluation period. This analysis will be performed on all individual cohorts separately. A similar analysis will be performed after defining the EOI nadir as the smallest value between the 110 minute timepoint after the start of the andexanet infusion and the 5-minute time point after the end of the continuous infusion.

The occurrence of thrombin generation above the lower limit of the normal range at its EOI peak, where EOI peak is defined as the largest value for thrombin generation between 110 minutes after the start of the andexanet infusion and ending 5 minutes after the end of the andexanet infusion, and the lower limit of normal range is defined as Mean–1SD of thrombin generation at Day 1 will be presented. A similar analysis will be performed for the occurrence of thrombin generation above the lower limit of the normal range at its EOB peak.

8.0 PHARMACOKINETIC ANALYSES

For Part 2 of the study, the plasma concentration results will be summarized by Day (for FXa inhibitors) and Cohort using descriptive statistics (N, mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, median, Min, and Max) and presented for the PK Population. Individual Subject-level plasma concentration data will be listed.

Non-compartmental PK analysis will be used for individual plasma concentration time values for all subjects. The andexanet dose used for this non-compartmental PK analysis will be the total (bolus plus infusion) dose administered to subjects. Descriptive statistics for all PK parameters determined this way will be presented by Cohort (N, mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, median, Min, and Max). The primary endpoint for andexanet PK evaluation will $AUC_{(0-\infty)}$ based on the PK population.

BLQ values will be imputed to zero prior to calculation of descriptive statistics for plasma concentration, except for the geometric mean calculation, where the log value will be assumed to be 0. Actual elapsed time from dosing will be used to estimate all individual plasma PK parameters.

9.0 SAFETY

The following sections describe how the safety endpoints will be analyzed. Safety analyses will be performed on the Safety Population. Safety analyses will be performed for the period during and after andexanet/placebo has been administered. Adverse events for subjects who received one or more doses of fXa inhibitor but discontinued prior to receiving study drug will be excluded from the analysis, but will be presented in a listing.

9.1. Extent of Exposure

The exposure of FXa inhibitor will be presented by cohort and treatment groups using summary statistics.

Dosing information for each drug (andexanet or placebo) and each subject will be listed, including dose assigned and total dose received. Interruptions or discontinuation of dosing will be listed by treatment received. The primary reason for study drug discontinuation will also be summarized by treatment received.

9.2. Adverse Events

Treatment-Emergent Adverse Events (TEAEs) will be summarized by cohort, treatment group, system organ class, and preferred term. System organ class and preferred term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 21.1). Treatment-Emergent Adverse Events are defined as any adverse event that occurred or worsened after andexanet/placebo dosing.

The number of events, the number of subjects, and the percentage of subjects who experienced at least one TEAE will be presented by cohort and treatment group. TEAEs that are considered by the investigator to be related to study medication, TEAEs that lead to early withdrawals, and serious TEAEs will be summarized in the same manner. Number and percentage of subjects in various severity categories (mild, moderate, severe, life-threatening, and fatal) will also be presented by cohort and treatment group.

The treatment groups will be compared with regards to safety endpoints descriptively. No inferential comparison will be conducted.

Besides the treatment emergent adverse events, an overall summary of pre-treatment adverse events, defined as those adverse events occurring after first dose of the FXa inhibitor but before exposure to andexanet or placebo.

9.3. Clinical Laboratory Assessments

Clinical laboratory parameters including hematology, chemistry, urinalyses, will be summarized by cohort, treatment group and by time point.

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Coagulation markers (F1+2, TAT, D-dimer and TFPI activity) will be summarized by cohort, treatment group and by time point, and presented graphically.

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

Hematology, chemistry and urinalysis values outside of normal ranges and/or with potential clinical importance (PCI) will be listed by subject, visit and treatment.

The antibodies (anti-andexanet, anti-fX, anti-fXa, HCP and/or neutralizing antibodies) will be summarized by cohort, treatment group, and study visit. A listing for subjects will also be provided.

9.4. Electrocardiogram (ECG)

A resting supine 12-lead ECG will be conducted at the Screening Visit, prior to the first study treatment, and post study treatment visits, and the results will be evaluated by the Investigator. ECG parameters include:

- Heart Rate (beats per minute)
- RR Duration (msec)
- PR Duration (msec)
- QRS Duration (msec)
- QT Duration (msec)
- QTcF—Fridericia's Correction Formula

The qualitative assessment of the overall ECG test results will be defined as:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant
- An outlier analysis will also be performed based on the proportion of subjects with treatment emergent values that meet the following criteria:
  - QTcF > 500 msec at any time point
  - QTcF increased by > 60 msec at any time point
  - PR > 220 msec at any time point

These abnormal values will be flagged in the listings.

9.5. Vital Signs and Oxygen Saturation

Vital signs include:

- Respiratory Rate (breaths per minute)
- Temperature (°F)
- Systolic Blood Pressure (mm Hg)
- Diastolic Blood Pressure (mm Hg)
- Heart Rate (beats per minute)
- Oxygen Saturation (%)

An analysis of abnormal values will be performed based on the proportion of subjects with treatment emergent values that meet the following criteria:

- SBP > 160 mmHg or < 90 mmHg
- DBP > 95 mmHg or < 50 mmHg
- HR < 45 or > 100
- O_2 Saturation < 92%

These abnormal values will be flagged in the listings sorted by subject number and parameter. All data (including unscheduled visits) will also be listed.

9.6. Physical Examination

Physical exam results will be presented in a listing that will be sorted, subject, parameter, and study visit.

9.7. Venous Thromboembolism (VTE)

Any report of DVT or pulmonary embolism from the Wells Score will be summarized and listed. This listing will be sorted by subject number and relative day.

10.0 ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines [1]. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation.
2. SAS program name, including the path that generates the output.
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all subjects combined. Row entries in tables are made only if data exists for at least one subject (i.e., a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

Supportive individual Subject Data Listings will be sorted and presented, subject number and visit date, if applicable. Listings will also include the number of days relative to the initial exposure to the study drug, if applicable.

Specific algorithms are discussed for imputing missing or partially missing dates, if deemed appropriate, under specific data topics. Imputed or derived data are flagged in the individual subject data listings. Imputed data will not be incorporated into any raw or primary datasets. The imputed data will be retained in the derived/analysis datasets along with flags of imputations. Imputations should be clearly described in the tables' footnotes.

The total duration for a subject *on study* will be calculated as the difference between the date of initial exposure to the study drug and the last day of observation plus one day. All calculations for defining the duration on study will follow the algorithm:

Duration = [Study Completion or Withdraw Date – Initial Drug Administration Date + 1].

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses:

- Summary statistics will consist of the number and percentage of responses in each level for categorical variables, and the sample size (n) mean, median, standard deviation (SD), minimum, and maximum values for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.

- The number and percentage of responses will be presented in the form XX (XX.X%).
- If presented, p-values will be rounded to 4 decimal places. All p-values that round to 0.000 will be presented as '< 0.001' and p-values that round to 1.00 will be presented as '> 0.999'. Probability values ≤ 0.05 will be considered to be statistically significant. The method used to calculate p-values need to be mentioned in the footnotes.
- All summary tables will include the analysis population sample size (i.e., number of subjects).
- Baseline values will be defined as those values recorded closest to, but prior to, the first study treatment on Day 6 (day of initiation of andexanet or placebo dosing).
- Change from baseline will be calculated as follows:

$$\text{Change} = \text{Post-baseline value} - \text{baseline value}$$

- Date variables will be formatted as DDMMMYYYY for presentation.
- SAS Version 9.3 [2] or higher will be the statistical software package used for all data analyses.
- The cohort, study treatment, and subject number will be included in all data listings. All listings will be sorted by study cohort, subject number, treatment, and visit date, as applicable.

11.0 REFERENCES

1. ICH E3: Structure and Content of Clinical Study Reports
2. SAS Institute Inc., SAS® Version 9.3 software, Cary, NC.