Statistical Analysis Plan

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of a Single Dose of E-WE Thrombin, Administered During a Regular Hemodialysis Procedure, in Patients with End-Stage Renal Disease on Chronic Hemodialysis

Protocol No: EWE-19-02
US IND No.: 18154
Final Protocol Date: 15 March 2019
Amendment One Date: 01 May 2019

Compound Name: E-WE thrombin (AB002)

Celerion Project CA26622
Final Version 1.0
Date: 18 September 2019

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Statistical Analysis Plan Signature Page

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Table of Contents

1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within the protocol, after the unblinding, or locking of the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data. Note that the header for this page will be the one used for the main body of the CSR.

Any additional exploratory analyses not addressed within this statistical analysis plan (SAP) and/or driven by the data, or requested by Aronora Inc., will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

The primary objective of the study is:

- To assess the safety and tolerability of a single dose of E-WE thrombin infused into the dialysis line during a 4-hour hemodialysis (HD) procedure in patients with end stage renal disease (ESRD).

The secondary objectives of the study are as follows:

- To assess the pharmacodynamics (PD) of a single dose of E-WE thrombin infused into the dialysis line during a 4-hour HD procedure in patients with ESRD. Activated protein C/protein C inhibitor complex (APC-PCI) will be used as a surrogate biomarker for drug exposure.

- To assess the efficacy of a single dose of E-WE thrombin infused into the dialysis line during a 4-hour HD procedure in patients with ESRD. Efficacy will be assessed by thrombus accumulation within the dialyzer cartridge (evaluated by visual inspection) and measurement of urea removed by 4 hours of dialysis (Kt/V and URR).

Note: Kt/V = volume of fluid completely cleared of urea [K = dialyzer clearance (mL/min), t = time of dialysis] and V = volume of water a patient's body contains.

URR = Urea reduction ratio

Formulas to calculate Kt/V and URR are located in Section 6.1.2.

2.2 Endpoints

Primary outcome measures:

- The safety and tolerability of E-WE thrombin following administration of the active treatment will be evaluated versus pre-treatment and placebo by number and severity of AEs (including HD vascular access site reactions), physical examinations, bleeding time from the HD vascular access sites, vital sign measurements, 12-lead ECGs, clinical laboratory tests, and coagulation tests.

Secondary outcome measures:

- Pharmacodynamics of E-WE thrombin will be measured by APC-PCI and plasma APC-PCI will act as a surrogate marker for E-WE thrombin drug exposure.
- Efficacy of antithrombotic activity will be evaluated by thrombus accumulation within the dialyzer cartridge (evaluated by visual inspection) after E-WE thrombin active treatment versus pre-treatment and placebo.
- Efficiency of HD will be assessed using BUN levels before and after dialysis to determine urea removed by 4 hours of dialysis (Kt/V and URR) after E-WE thrombin active treatment versus pre-treatment and placebo.

Other outcome measures:

- Development of antibodies to E-WE thrombin or WT thrombin after drug exposure.

3. STUDY DESIGN

This is a phase 2, randomized, double-blind, placebo-controlled, single-dose study of E-WE thrombin designed to evaluate the safety and efficacy at 2 dose levels administered to patients with ESRD during HD conducted at one study centre in the US.

Patients will be enrolled in Cohort 1 or Cohort 2; cohorts will be dosed sequentially. Dosing of Cohort 2 will commence following completion of all study events for all patients in Cohort 1. Within each cohort, patients will be randomized to receive active drug or matching placebo as summarized below:

Table 1. Cohort and Treatment Randomization

Cohort	Treatment	Active:Placebo	Cohort Size
1	0.5 µg/kg bolus dose administered into the dialysis line immediately followed by a 0.25 µg/kg/hour continuous infusion dose into the dialysis line over 4 hours of E-WE thrombin or matching placebo, for a total dose of 1.5 µg/kg	2:1	12:6
2	1 µg/kg bolus dose administered into the dialysis line immediately followed by a 0.5 µg/kg/hour continuous infusion dose into the dialysis line over 4 hours of E-WE thrombin or matching placebo, for a total dose of 3 µg/kg	2:1	12:6

This study includes a screening period of 28 days prior to checking in to the CRU on Day -8. From Day -8 (8 days prior to dosing on Day 1) through Day 3, all patients will undergo HD five times and will be assessed for all scheduled procedures and endpoints before and after each HD session, using only one type of dialyzer cartridge for each patient.

On Day 1, prior to dosing, patients will undergo baseline measurements followed by initiation of a regular HD procedure, consistently using only one type of dialyzer cartridge for each patient. A single dose of E-WE thrombin or matching placebo will be administered into the dialysis line during the HD procedure. Patients will continue to undergo HD procedures and scheduled assessments from Day 1 through Day 3.

Study assessments will include AEs, including HD vascular access site (AV fistula or AV graft) reactions, physical examinations, vital sign measurements, 12-lead ECGs, clinical laboratory tests, coagulation tests, immunogenicity assessments, and PD blood sampling for APC-PCI and measurement of urea removed by 4 hours of dialysis to be performed throughout the study. On Days -7, -5, -2, 1, and 3, bleeding time from the HD vascular access sites on the AV fistula or AV graft (ladder or buttonhole technique) will be evaluated immediately at the end of the HD session. The dialyzer cartridge will be rinsed, visually inspected and graded against a standardized visual assessment scale at the end of the HD procedure, and photographed on 4 sides.

Additionally, plasma and dialysate samples will be collected and sent to Sponsor along with the used and rinsed dialyzer cartridges for potential internal evaluation of plasma protein C, dialysate urea, and total protein accumulation within the dialyzer cartridge.

All patients who receive the study drug or matching placebo (including patients who terminate the study early) will return to the CRU on Day 14 (± 2 days) for coagulation tests, immunogenicity sample collection, and to determine if any AE has occurred since the last study visit.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Safety Population

All patients who received the study drug (active or matching placebo) will be included in the safety evaluations.

Pharmacodynamic Population

All patients who received the study drug (active or placebo) and had at least one postdose measurement of any of the PD assessment will be included in the PD evaluation.

4.2 Preliminary Data and Interim Analysis

Celerion has not been contracted to complete any interim safety and PD analyses.

5. TREATMENT DESCRIPTIONS

Patients will receive a total dose of either 1.5 µg/kg E-WE thrombin, 3.0 µg/kg E-WE thrombin, or matching placebo on Day 1.

Planned doses for each cohort of the study are as follows:

Cohort 1: Total dose of 1.5 µg/kg E-WE thrombin or matching placebo on Day 1
Cohort 2: Total dose of 3.0 µg/kg E-WE thrombin or matching placebo on Day 1

The patients' weight recorded at check-in will be used to calculate the study drug dose.

Treatments will be described as follows:

Cohort	Treatment	Short Description (used in text)	Long Description (used in Tables Figures and Listings)
Cohorts 1 & 2	P	Placebo (Pooled)	0.5/1.0 µg/kg bolus dose of matching placebo followed by a 0.25/0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5/3.0 µg/kg (Pooled matching placebo of Treatments A and B)
Cohort 1	A	1.5 µg/kg E-WE thrombin	0.5 µg/kg bolus dose of E-WE thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
Cohort 2	B	3.0 µg/kg E-WE thrombin	1.0 µg/kg bolus dose of E-WE thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg

6. PHARMACODYNAMIC ANALYSIS

Plasma APC-PCI will be measured as a surrogate biomarker of drug exposure. APC-PCI will be used to detect the magnitude and duration of action of E-WE thrombin.

No pharmacokinetic (PK) or statistical analysis will be required for APC-PCI. Individual, mean, and median data for APC-PCI will be presented graphically for all treatments (2 active dose levels and pooled placebo).

6.1 Pharmacodynamic Assessment

Pharmacodynamic assessments will include evaluation of the efficacy of E-WE thrombin and the efficiency of HD.

6.1.1 Drug Efficacy

Efficacy of antithrombotic activity will be evaluated by thrombus accumulation within the dialyzer. Thrombus accumulation will be evaluated by visual inspection of the venous chamber and dialyzer membrane at the end of HD procedures and by a gradation using a standardized visual assessment scale. The dialyzer cartridge will be rinsed, visually inspected, graded, and photographed on 4 sides. The dialysis venous chamber will be visually inspected, graded and photographed. The number of dialyzer cartridges used for each HD session will be recorded.

Visual inspection of clotting in dialysis venous chamber will be recorded at the end of dialysis on Days -7, -5, -2, 1, and 3 with the following categories:

1 = No detectable clotting
2 = Presence of fibrinous ring or minimum clot affecting less than 5% of chamber space
3 = Clot formation (affecting more than 5% of but less than 25% of chamber space)
4 = Clot formation (affecting more than 25% of but less than 50% of chamber space)
5 = Clot formation (affecting more than 50% of but less than 75% of chamber space)
6 = Clot formation (affecting more than 75% of chamber space)
7 = Occluded (also assess the category of clot that caused occlusion)

Visual inspection of clotting in the dialysis filter will be recorded at the end of dialysis on Days -7, -5, -2, 1, and 3 with the following categories:

1 = No clotting, clean filter or few blood streaks (affecting less than 5% of the fibers seen at the surface of dialyzer),
2 = Blood streaks affecting more than 5% but less than 25 % of the fibers seen at the surface of the dialyzer,
3 = Blood streaks affecting more than 25% but less than 50 % of the fibers seen at the surface of the dialyzer,
4 = Blood streaks affecting more than 50% but less than 75 % of the fibers seen at the surface of the dialyzer,
5 = Blood streaks affecting more than 75% of the fibers seen at the surface if the dialyzer,
6 = Occluded (also assess the category of streaking at the time of occlusion)

Clotting categories will be listed and frequency summarized by Treatment and Day for all subjects in the Safety Population (2 active dose levels and pooled placebo).

Note: Plasma and dialysate samples will be frozen and sent to Sponsor along with the used and rinsed dialyzer cartridges and venous drip chambers for potential internal evaluation of plasma protein C, dialysate urea, and total protein accumulation within the dialyzer cartridge. Dialysate samples will be stored for up to 5 years following the last dosing for future analysis.

6.1.2 Efficiency of HD

Efficiency of HD will be assessed by using blood urea nitrogen (BUN) levels before and after dialysis to determine urea removed by 4 hours of dialysis (Kt/V and URR) after E-WE thrombin active treatment versus pre-treatment and placebo.

BUN: Samples for BUN will be collected pre- and post-dialysis on Days -7, -5, -2, 1, and 3.

The change in BUN values on Days -7, -5, -2, 1, and 3 will be calculated by subtracting the post-dialysis BUN from the pre-dialysis BUN values for each day separately. BUN values will be listed and summarized by treatment and Day in tables and figures for all subjects in the PD Population (2 active dose levels and pooled placebo).

URR and Kt/V: The derived PD parameters urea reduction ratio (URR) and Kt/V will be calculated from the pre- and post-dialysis BUN values on Days -7, -5, -2, 1, and 3.
URR will be calculated using the following formula:

URR = (1-(post-dialysis BUN/ pre-dialysis BUN))*100

Kt/V will be calculated using the following formula:

$$sp\frac{Kt}{V} = -\ln(R - (0.008 \times t)) + (4 - (3.5 \times R)) \times \frac{UF}{Wt}$$

Where R = BUN Post-dialysis/BUN Pre-dialysis
t = Time of HD
UF = Pre-dialysis patient weight – Post-dialysis patient weight
Wt = Post-dialysis weight of patient.

URR and Kt/V values will be listed and summarized by treatment and Day in tables for all subjects in the PD Population (2 active dose levels and pooled placebo).

6.1.3 Internal Analysis by the Sponsor:

The following analyses may be performed by the Sponsor for internal purposes; these results may be included in the appendices of the CSR.

- Protein C Analysis
- Dialysate Analysis
- Analysis of Protein Accumulation Within the Dialyzer Cartridge

Full details are located in the protocol.

6.2 Measurements and Collection Schedule

APC-PCI: For all patients, blood samples for the determination of APC-PCI will be collected on Day 1 at predose (hour 0, at least 1 hour prior the start of HD session) and at 0.167, 0.5, 1, 2, 4, 6, and 24 hours after E-WE thrombin bolus dose.

All APC-PCI concentration data will be included in the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

Protein C: For all patients, blood samples for the determination of protein C will be collected at the start and end of dialysis on Days -7, -5, -2 and 3. On Day 1, samples will be collected at predose (hour 0, at least 1 hour prior the start of HD session) and at 0.167, 0.5, 1, 2, 4, 6, and 24 hours after E-WE thrombin bolus dose.

6.3 Bioanalytical Method

Plasma concentrations of APC-PCI will be determined using an enzyme-linked immunosorbent assay (ELISA) validated with respect to accuracy, precision, linearity, sensitivity, and specificity at Celerion, Lincoln, Nebraska. The analytical range (lower limit of quantitation [LLOQ] – upper limit of quantitation [ULOQ]) for APC-PCI is expected to be 0.02 – 1.00 ng/mL.

Blood samples for protein C will be shipped to Aronora.

6.4 Investigational Product and PD Analyte Information

6.4.1 E-WE Thrombin (APC-PCI)

E-WE thrombin is a purified protein produced by recombinant DNA technology in a bacterial (Escherichia coli) cell culture system. Injection of E-WE thrombin results in the temporal and selective generation of endogenous APC and subsequent escape of some of this endogenous APC into the blood circulation. In vitro, in the presence of phospholipid membranes, APC inactivates factor Va and factor VIIIa, resulting in a temporal prolongation of the aPTT that is observed at higher doses of E-WE thrombin.

6.5 APC-PCI Concentrations

Plasma concentrations of APC-PCI as determined at the collection times and per the bioanalytical method described in Section 6.2 and Section 6.3, respectively, will be presented graphically for all treatments (2 active dose levels and pooled placebo).

6.6 Data Summarization and Presentation

6.6.1 APC-PCI

All plasma APC-PCI concentrations and descriptive statistics will be generated using SAS® version 9.3 or higher. A concentration table will be presented for pooled placebo samples without descriptive statistics.

Plasma concentrations of APC-PCI will be listed and summarized by treatment and time points for all subjects in the PD population. Plasma concentrations will be presented with the same level of precision as received from the bioanalytical laboratory. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration time points. Excluded subjects will be included in the concentration listings, but will be excluded from the summary statistics and noted as such in the tables.

For the calculation of APC-PCI summary statistics, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration will be set to 0 and as missing elsewhere. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly.

Mean, median, and individual concentration-time profiles will be presented on linear scale. Linear mean plots will be presented with and without SD.

The level of precision for APC-PCI, URR, and Kt/Vsummary statistic will be presented as follows:

- Minimum/maximum: in same precision as in the bioanalytical/clinical laboratory database
- Mean/median: in one more level of precision than minimum/maximum
- SD/SEM: in one more level of precision than Mean/median
- n will be presented as an integer
- CV% will be presented to the nearest tenth

7. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment time points. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum. Data from subjects who received the placebo treatment will be pooled across cohorts.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer. Percentages of total frequency counts, if presented, will be reported as whole numbers.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.1 Subject Discontinuation

Subjects will be summarized by number of subjects dosed, completed, and discontinued the study with discontinuation reasons by treatment (two dose levels and pooled placebo) and study overall.

7.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) and frequency counts will be provided for categorical variables (race, ethnicity, and sex) by treatment and overall. Age will be derived from date of birth to date of informed consent.

7.3 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.1.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, severity, relationship to study medication, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to a treatment based on the onset date and time of the AE. If the onset time of an AE is missing and the onset date is the same as the treatment dosing date, then the AE will be considered treatment emergent. If the onset date of an AE is missing, then the AE will be considered treatment emergent.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of number of subjects dosed by treatment and overall. The number of AEs will be tabulated in a similar manner. Tables which tabulate the number of TEAEs by severity and relationship to study treatment will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

7.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, Coagulation and Urinalysis)

Safety serum chemistry, hematology and urinalysis tests are performed at Screening, Day -8 check-in, and end of HD on Day 3. For anuric patients, urinalysis may not be performed. Coagulation is collected at Screening, Day -8 check-in, start and end of

HD on Days -7, -5, -2, 1, and 3, and at Follow-up. Platelet count is collected at start and end of HD on Days -7, -5, -2, 1, and 3.

Out-of-range values and clinically significant results will be listed.

For serum chemistry and hematology laboratory values, descriptive statistics will be presented for each laboratory test by assessment time point and treatment. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest and prior to dose which may include unscheduled results. This will typically be the result collected at Day -8 check-in. Postdose unscheduled events or early termination results will not be included in summaries.

For each serum chemistry and hematology laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective postdose results.

For coagulation tests (aPTT, PT/INR, fibrinogen, and TT) and platelet count on HD days, summary will be for pre- and post-HD and fold change. Coagulation parameters and platelet count will be listed and presented together since they have the same timepoints. Urinalysis test results will be listed only.

7.5 Vital Signs

Vital signs tests (HR, BP, RR and T) will be assessed at Screening, Day -8 check-in, within one hour prior to start of HD on Days -7, -5, -2, 1 and 3 and 1 hour postdose on Day 1.

Vital sign results will be summarized by treatment and time point. Change from baseline will be summarized in a similar way. Baseline is defined as the result closest and prior to the dose on Day 1, which may include unscheduled results, whichever is later. Postdose unscheduled events will not be included in summaries.

7.6 Weight

Weight will be assessed at Screening, Day -8 check-in, at start and end of HD on Days -7, -5, -2, 1 and 3. Weight will be summarized by treatment and time point.

7.7 Electrocardiogram

Safety ECGs (HR, PR, QRS, QT and Fridericia correction QTcF) will be assessed at Screening, Day -8 check-in, Hour 0.5 postdose Day 1 and end of HD on Day 3.

ECG parameters will be summarized by dose level, pooled placebo, and time point. Change from baseline will be summarized in a similar way. Baseline is defined as the result closest and prior to the dose from Day -8 check-in, which may include unscheduled results, whichever is later. Postdose unscheduled events will not be included in summaries.

The QTcF values that are > 450 ms and increase from baseline > 30 ms will be flagged in the data listings.

7.8 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary Version September 2018, B3 and listed.

7.9 Physical Examination

Full physical examinations will be performed at Screening, Day -8 check-in and end of HD on Day 3. Abbreviated physical examination will be performed at Hour 0.167 on Day 1 or at other times, at the PI's or designee's discretion. Abnormal findings will be reported as medical history or adverse events. All data found in the CRF will be listed.

7.10 Vascular Access Site Reaction

Vascular access site reaction will be assessed at predose and 4 hours post dose on Day 1 and at start and 20 minutes post HD on Day 3. Any new abnormal findings inconsistent with past skin injuries as expected in patient on chronic HD will be reported and summarized as AEs. All data collected on the CRF will be listed.

7.11 Bleeding Time

The time to clot (bleeding time) will be recorded following hemodialysis after the needle is removed from the vascular access site on Days -7, -5, -2, 1, and 3. Summary statistics will be calculated for time to clot by treatment and assessment timepoint.

7.12 Medical History

All medical and surgical histories recorded in the study will be coded with MedDRA®, Version 21.1, and listed.

7.13 Immunogenicity

Blood samples for immunogenicity assessment will be performed at predose on Day 1 and follow-up. Data will be provided as an appendix.

8. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

9. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all PD, immunogenicity and Safety summary tables and figures will be generated using SAS® Version 9.3 or

higher and/or using Phoenix® WinNonlin® Version 7.0 or higher for summary PD TFLs, as appropriate.

9.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1 Subject Disposition Summary

Section 11:

Tables

Table 11-1 Demographic Summary

Table 11-2 Summary of Clotting in the Dialysis Venous Chamber – Days -7 to 3 (PD Population)

Table 11-3 Summary of Clotting in the Dialysis Filter – Days -7 to 3 (PD Population)

Table 11-4 Summary of Difference Between Pre- and Post-dialysis BUN and URR – Days -7 to 3 (PD Population)

Table 11-5 Summary of Kt/V Values (PD Population)

Figures

Figure 11-1 Arithmetic Mean Plasma APC-PCI Concentration Versus Time Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)

Figure 11-2 Median Plasma APC-PCI Concentration Versus Time Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)

Figure 11-3 Arithmetic Mean Pre- and Post-dialysis BUN Values Versus Time – Days -7 to 3 (Linear Scale) (PD Population)

Section 12:

Table 12-1 Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event (% of Subjects Dosed)

9.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be re-numbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

Table 14.1.1 Summary of Disposition (Safety Population)
Table 14.1.2 Summary of Demographics (Safety Population)

14.2 Pharmacodynamic Data Summary Tables and Figures

14.2.1. Plasma APC-PCI Tables and Figures

Table 14.2.1.1.1 Plasma APC-PCI Concentrations (unit) Following Administration of 1.5 µg/kg E-WE Thrombin – Day 1 (PD Population)
Table 14.2.1.1.2 Plasma APC-PCI Concentrations (ng/mL) Following Administration of 3.0 µg/kg E-WE Thrombin – Day 1 (PD Population)
Table 14.2.1.1.3 Plasma APC-PCI Concentrations (ng/mL) Following Administration of Placebo – Day 1 (Pooled)
Figure 14.2.1.2.1 Arithmetic Mean (SD) Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)
Figure 14.2.1.2.2 Arithmetic Mean Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)
Figure 14.2.1.2.3 Median Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)

14.2.2 Clotting in the Dialysis Venous Chamber Tables

Table 14.2.2.1 Frequency of Clotting in the Dialysis Venous Chamber Days -7 to 3 (PD Population)

14.2.3 Clotting in Dialysis Filter Tables

Table 14.2.3.1 Frequency of Clotting in the Dialysis Filter Days -7 to 3 (PD Population)

14.2.4 BUN Tables and Figures

Table 14.2.4.1.1 Individual and Mean Difference between Pre- and Post-dialysis BUN Values (unit) and URR – Days -7 to 3 – 1.5 µg/kg E-WE Thrombin on Day 1 (PD Population)

Table 14.2.4.1.2 Individual and Mean Difference between Pre- and Post-dialysis BUN Values (unit) and URR – Days -7 to 3 – 3.0 µg/kg E-WE Thrombin on Day 1 (PD Population)

Table 14.2.4.1.3 Individual and Mean Difference between Pre- and Post-dialysis BUN Values (unit) and URR – Days -7 to 3 – Placebo (Pooled) (PD Population)

Programmer Note: ***For Tables 14.2.4.1.1 through 14.2.4.1.3, the difference will be calculated as follows: (Pre-dialysis – Post-dialysis).***

Figure 14.2.4.2.1 Arithmetic Mean (SD) Pre- and Post-dialysis BUN Values – Days -7 to 3 (Linear Scale) (PD Population)

Figure 14.2.4.2.2 Arithmetic Mean Pre- and Post-dialysis BUN Values – Days -7 to 3 (Linear Scale) (PD Population)

14.2.5 Kt/V Tables

Table 14.2.5.1.1 Individual and Mean Kt/V Values (unit) – 1.5 µg/kg E-WE Thrombin on Day 1 (PD Population)

Table 14.2.5.1.2 Individual and Mean Kt/V Values (unit) – 3.0 µg/kg E-WE Thrombin on Day 1 (PD Population)

Table 14.2.5.1.3 Individual and Mean Kt/V Values (unit) – Placebo (Pooled) (PD Population)

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Treatment-emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subject Dosed) (Safety Population)

Table 14.3.1.2 Treatment-emergent Adverse Event Frequency by Treatment – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Table 14.3.1.3 Treatment-emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Drug – Number of Adverse Events (Safety Population)

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events (Safety Population)

<if no serious adverse event occurred, a statement 'No serious adverse event is reported'>

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology/Coagulation (Safety Population)

Table 14.3.4.3 Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.2 Clinical Laboratory Shift from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.3 Clinical Laboratory Summary and Change from Baseline – Hematology (Safety Population)

Table 14.3.5.4 Clinical Laboratory Shift from Baseline – Hematology (Safety Population)

Table 14.3.5.5 Clinical Laboratory Summary and Change from Baseline – Coagulation and Platelet Count (Safety Population)

Table 14.3.5.6 Vital Sign Summary and Change from Baseline (Safety Population)

Table 14.3.5.7 Summarization of Weight (Safety Population)

Table 14.3.5.8 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

Table 14.3.5.9 Summarization of Bleeding Time (Safety Population)

9.3 Section 16 Data Listings

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

Appendix 16.1.9 Statistical Methods

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1 Study Completion/Early Termination (Safety Population)

16.2.2 Protocol Deviations

Appendix 16.2.2 Protocol Deviations

16.2.3 Subjects Excluded from Pharmacodynamic Analyses

Appendix 16.2.3 Subjects Excluded from Pharmacodynamic Analyses

<Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.>

16.2.4 Demographic Data

Appendix 16.2.4.1 Demographics (Safety Population)
Appendix 16.2.4.2 Physical Examination (Safety Population)
Appendix 16.2.4.3 Medical and Surgical History (Safety Population)
Appendix 16.2.4.4 Alcohol Screen (Safety Population)
Appendix 16.2.4.5 Saliva Drug Screen (Safety Population)
Appendix 16.2.4.6 Tobacco Use (Safety Population)

16.2.5 Compliance and/or Drug Concentration Data

Appendix 16.2.5.1 Subject Eligibility at Screening (Safety Population)
Appendix 16.2.5.2 Subject Eligibility at Check-In (Safety Population)
Appendix 16.2.5.3 Test Compound Administration (Safety Population)

Appendix 16.2.5.4 Blood Draw Times for E-WE Thrombin PD (APC-PCI) (Safety Population)
Appendix 16.2.5.5 Blood Draw Times for Protein C (Safety Population)
Appendix 16.2.5.6 Blood Draw Times for Immunogenicity (Safety Population)
Appendix 16.2.5.7 Blood Draw Times for Dialysate Analysis for Kt/V and URR (Safety Population)
Appendix 16.2.5.8 Dialysate Collection (Safety Population)
Appendix 16.2.5.9.1 Dialyzer Assessment (I of V) – Hemodialysis Start and End Times (Safety Population)
Appendix 16.2.5.9.2 Dialyzer Assessment (II of V) - Circuit Arterial and Venous Pressure and Blood Flow Rate (Safety Population)
Appendix 16.2.5.9.3 Dialyzer Assessment (III of V) –Number and Volume of Saline Flushes (Safety Population)
Appendix 16.2.5.9.4 Dialyzer Assessment (IV of V) – Clotting in Dialysis Venous Chamber (Safety Population)
Appendix 16.2.5.9.5 Dialyzer Assessment (V of V) – Clotting in Dialysis Filter (Safety Population)
Appendix 16.2.5.10 Non-Study Procedures (Safety Population)
Appendix 16.2.5.11 Prior and On-Study Concomitant Medications (Safety Population)

16.2.6 Individual Pharmacodynamic Response Data

Individual APC-PCI Figures

Appendix 16.2.6.1.1 Individual Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 µg/kg E-WE Thrombin (Linear) for <Subject #>

Appendix 16.2.6.1.2 Individual Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 3.0 µg/kg E-WE Thrombin (Linear) for <Subject #>

Individual BUN Figures

Appendix 16.2.6.2.1 Individual Pre- and Post-dialysis BUN Values Versus Time – Days -7 to 3 (Linear Scale) for <Subject #>

16.2.7 Adverse Events Listings

Appendix 16.2.7.1.1 Adverse Events (I of II) (Safety Population)
Appendix 16.2.7.1.2 Adverse Events (II of II) (Safety Population)

Appendix 16.2.7.2 Adverse Event Preferred Term Classification (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)

Appendix 16.2.8.1.2 Clinical Laboratory Report - Hematology (Safety Population)

Appendix 16.2.8.1.3 Clinical Laboratory Report – Coagulation and Platelet Count (Safety Population)

Appendix 16.2.8.1.4 Clinical Laboratory Report - Urinalysis (Safety Population)

Appendix 16.2.8.1.5 Clinical Laboratory Report – Additional Tests (Safety Population)

Appendix 16.2.8.1.6 Clinical Laboratory Report - Comments (Safety Population)

<Note: Appendices 16.2.8.1.5 and 16.2.8.1.6 will be removed if not applicable>

Appendix 16.2.8.2 Vital Signs (Safety Population)

Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

Appendix 16.2.8.4 Vascular Access Site Reaction Assessment (Safety Population)

10. TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all in-text tables will be presented in Times New Roman as close as possible to font size 12 to fit on a portrait page and all post-text tables will be presented in Courier New font size 9. These tables will be generated off of the Celerion ADaM structure. ADaM datasets are created in accordance with CDISC guidance (ADaM Model 2.1 and ADaM implementation guide 1.1).

10.1 In-text Summary Tables Shells

In-text Table 10-1 will be in the following format:

Table 10-1 Subject Disposition Summary

Table 10-1 Subject Disposition Summary (Safety Population)

Disposition	1.5 µg/kg E-WE Thrombin	3.0 µg/kg E-WE Thrombin	Placebo (Pooled)	Overall
Dosed	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Completed	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Discontinued	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Reason1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Reason2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)

Source: Table 14.1.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_disp.sas DDMMMYYYY HH:MM

In-text Table 11-1 will be in the following format:

Table 11-1 Demographic Summary

Trait	Category/ Statistics	1.5 µg/kg E-WE Thrombin	3.0 µg/kg E-WE Thrombin	Placebo (Pooled)	Overall
Sex	Male	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Female	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Race	Asian	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Black or African American	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	White	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Ethnicity	Hispanic or Latino	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
	Not Hispanic or Latino	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Age* (yrs)	n	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X
	Maximum	XX	XX	XX	XX
Weight (kg)	n	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X
	Maximum	XX	XX	XX	XX

*Age is calculated at the time of first dosing.
BMI = Body mass index

Source: Table 14.1.2
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM

Programmer note: also include height and BMI

Table 11-2 Summary of Clotting in the Dialysis Venous Chamber – Days -7 to 3 (PD Population)

Clotting in the Dialysis Venous Chamber																					
Time Point	Treatments																				
	1.5 µg/kg E-WE Thrombin							3.0 µg/kg E-WE Thrombin							Placebo (Pooled)						
	Category Post-dialysis [n=xx]							Category Post-dialysis [n=xx]							Category Post-dialysis [n=xx]						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Day -7	X	X	X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 1*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Category:
1 = No detectable clotting
2 = Presence of fibrinous ring or minimum clot affecting less than 5% of chamber space,
3 = Clot formation (affecting more than 5% of but less than 25% of chamber space),
4 = Clot formation (affecting more than 25% of but less than 50% of chamber space),
5 = Clot formation (affecting more than 50% of but less than 75% of chamber space),
6 = Clot formation (affecting more than 75% of chamber space),
7 = Occluded (also assess the category of clot that caused occlusion)

[a]-n=xx
* - Single IV doses of 1.5, 3.0 µg/kg E-WE Thrombin or placebo were administered on Day 1
Values will be presented as arithmetic mean

Source: Table 14.2.2.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

- n will be presented as an integer (with no decimal);
- Internal template ITPar1, with the following changes: n will be presented in the column title with more additional columns to be created.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Table 11-3 Summary of Clotting in the Dialysis Filter – Days -7 to 3 (PD Population)

Clotting in Dialysis Filter																		
Time Point	Treatments																	
	1.5 µg/kg E-WE Thrombin						3.0 µg/kg E-WE Thrombin						Placebo (Pooled)					
	Category Post-dialysis [n=xx]						Category Post-dialysis [n=xx]						Category Post-dialysis [n=xx]					
	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Day -7	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -5	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -2	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 1*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 3	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Category:
1 = No clotting, clean filter or few blood streaks (affecting less than 5% of the fibers seen at the surface of dialyzer),
2 = Blood streaks affecting more than 5% but less than 25 % of the fibers seen at the surface of the dialyzer,
3 = Blood streaks affecting more than 25% but less than 50 % of the fibers seen at the surface of the dialyzer,
4 = Blood streaks affecting more than 50% but less than 75 % of the fibers seen at the surface of the dialyzer,
5 = Blood streaks affecting more than 75% of the fibers seen at the surface if the dialyzer,
6 = Occluded (also assess the category of streaking at the time of occlusion)

[a]-n=xx
* - Single IV doses of 1.5, 3.0 µg/kg E-WE Thrombin or placebo were administered on Day 1
Values will be presented as arithmetic mean

Source: Table 14.2.3.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells
- Internal template ITPar1, with the following changes: n will be presented in the column title with more additional columns to be created.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Table 11-4 Summary of Difference between Pre- and Post-dialysis BUN and URR – Days -7 to 3 (PD Population)

Mean Blood Urea Nitrogen (Reference Range xx – xx <units>) and URR (Reference Range xx – xx <%>)												
Time Point	Treatments											
	1.5 µg/kg E-WE Thrombin				3.0 µg/kg E-WE Thrombin				Placebo (Pooled)			
	Pre-dialysis (Unit) [n=xx]	Post-dialysis (Unit) [n=xx]	Difference (Unit) [n=xx]	URR (%) (Unit) [n=xx]	Pre-dialysis (Unit) [n=xx]	Post-dialysis (Unit) [n=xx]	Difference (Unit) [n=xx]	URR (%) (Unit) [n=xx]	Pre-dialysis (Unit) [n=xx]	Post-dialysis (Unit) [n=xx]	Difference (Unit) [n=xx]	URR (%) (Unit) [n=xx]
Day -7	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X
Day -5	XXX.X[a]	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X
Day -2	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X
Day 1*	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X
Day 3	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X	XXX.X	XXX.X	XX.X	XX.X

Difference = Pre-dialysis - Post-dialysis
[a]-n = xx
URR = (1-(post-dialysis BUN/ pre-dialysis BUN))*100
* - Single IV doses of 1.5, 3.0 µg/kg E-WE Thrombin or placebo were administered on Day 1
Values will be presented as arithmetic mean

Source: Tables 14.2.4.1.1 through 14.2.4.1.3
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells
- Internal template ITPar1, with the following changes: n will be presented in the column title with more additional columns to be created.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Table 11-5 Summary of Kt/V Values (PD Population)

Single pool Kt/V															
Time Point	Treatments														
	1.5 µg/kg E-WE Thrombin					3.0 µg/kg E-WE Thrombin					Placebo (Pooled)				
	R (unit) [n=xx]	t (unit) [n=xx]	UF (unit) [n=xx]	Wt (unit) [n=xx]	Kt/V (unit) [n=xx]	R (unit) [n=xx]	t (unit) [n=xx]	UF (unit) [n=xx]	Wt (unit) [n=xx]	Kt/V (unit) [n=xx]	R (unit) [n=xx]	t (unit) [n=xx]	UF (unit) [n=xx]	Wt (unit) [n=xx]	Kt/V (unit) [n=xx]
Day -7	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Day -5	XX.X	XX.X	XX.X	XX.X[a]	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Day -2	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Day 1*	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Day 3	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

[a]-n=xx
* - Single IV doses of 1.5, 3.0 µg/kg E-WE Thrombin or placebo were administered on Day 1
Values will be presented as arithmetic mean

R= post-dialysis BUN/pre-dialysis BUN))*100
t = Time of HD
UF = Pre-dialysis Weight – Post-dialysis Weight
Wt = Post-dialysis weight of patient
$Kt/V = -\ln(R - (0.008 \times t)) + (4 - (3.5 \times R)) \times \frac{UF}{Wt}$

Source: Tables 14.2.5.1.1 through 14.2.5.1.3
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

- n will be presented as an integer (with no decimal);
- Summary statistics will be presented with same precision as defined in post-text shells
- Internal template ITPar1, with the following changes: n will be presented in the column title with more additional columns to be created.

Program: /CAXXXXX/sas_prg/pksas/intext-pk-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

In-text Table 12-1 will be in the following format:

Table 12-1 Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event (% of Subjects Dosed)

Adverse Event*	1.5 µg/kg E-WE Thrombin	3.0 µg/kg E-WE Thrombin	Placebo (Pooled)	Overall
Number of Subjects With TEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
Number of Subjects Without TEAEs	XX (XX%)	XX (XX%)	XX (XX%)	XX (XX%)
System Organ Class 1	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term 1	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term 2	X (X%)	X (X%)	X (X%)	X (X%)
System Organ Class 2	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term 1	X (X%)	X (X%)	X (X%)	X (X%)
Preferred Term 2	X (X%)	X (X%)	X (X%)	X (X%)

*Adverse events are classified according to MedDRA Version 21.1.
TEAEs = Treatment-emergent adverse events
If a subject has 2 or more clinical adverse events, the subject is counted only once within a category. The same subject may appear in different categories.

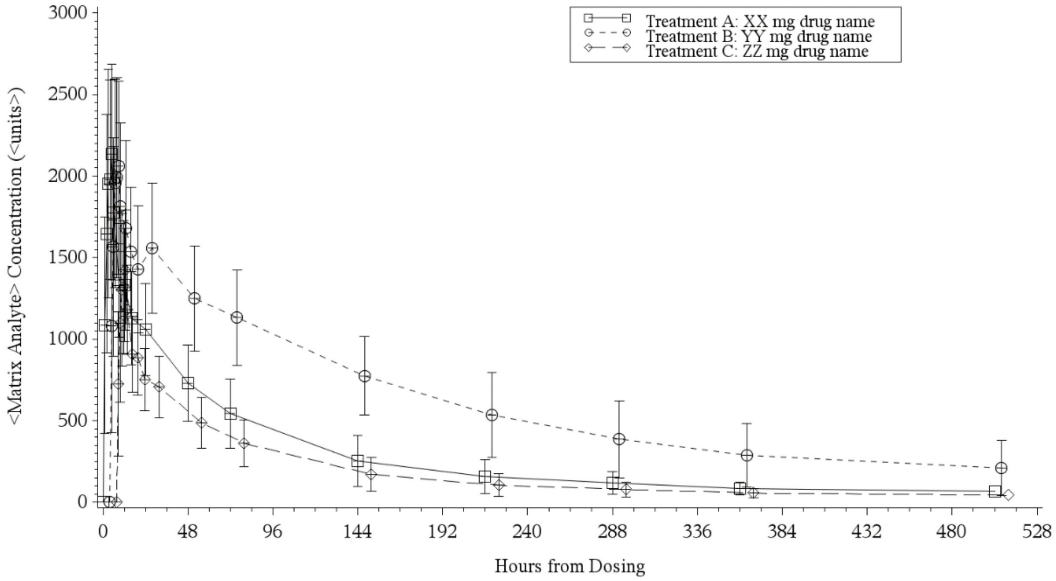
Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intext/t_ae.sas DDMMMYYYY HH:MM

10.2 Figures Shells

In-text Figures 11-1, 11-2, post-text Figures 14.2.1.2.1 through 14.2.1.2.3, and Individual Listings in 16.2.6.1.1, and 16.2.6.1.2, will be in the following format:

Figure 14.2.1.2.1

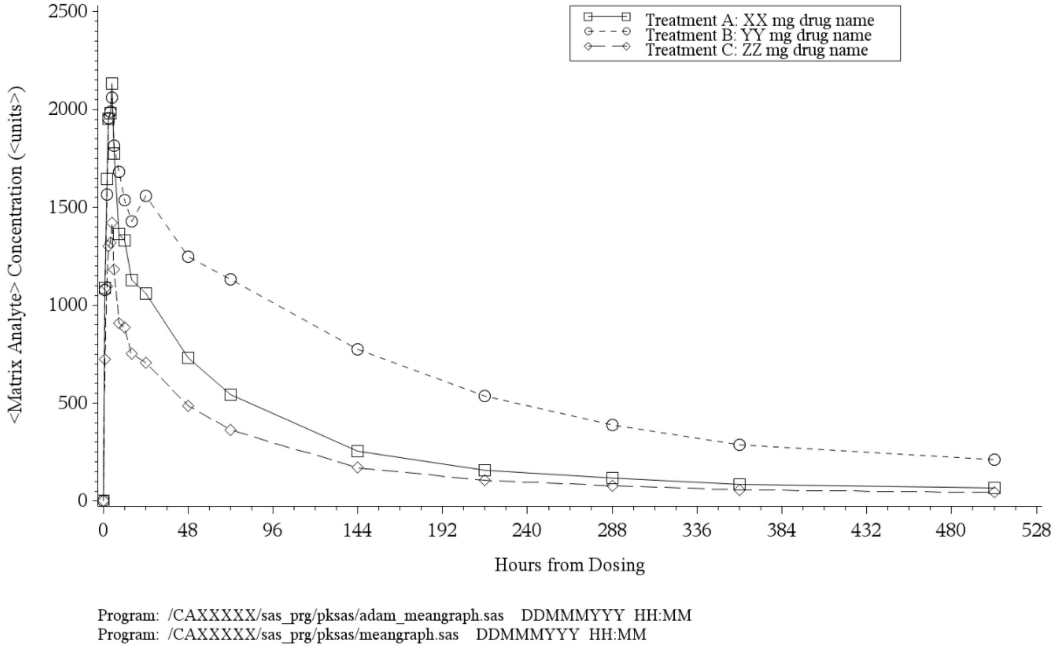
Arithmetic Mean (SD) Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)



Treatments B and C are shifted to the right for ease of reading
Program: /CAXXXXX/sas_prg/pksas/adam_meangraph.sas DDMMMYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/meangraph.sas DDMMMYYY HH:MM

Figure 14.2.1.2.2

Arithmetic Mean Plasma APC-PCI Concentration Versus Time Profiles Following Administration of 1.5 and 3.0 µg/kg E-WE Thrombin – Day 1 (Linear Scale) (PD Population)

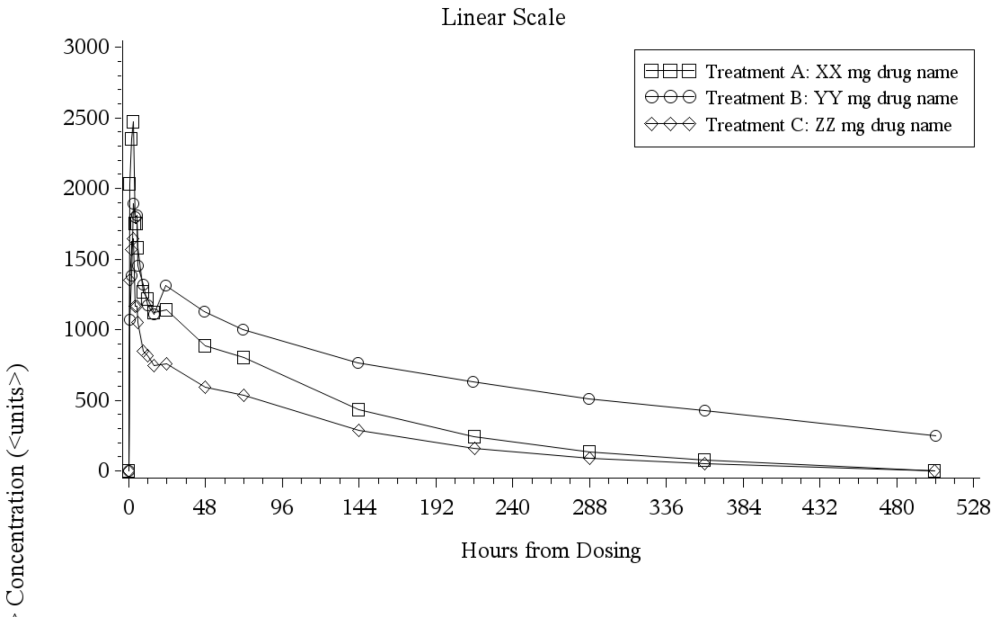


Figures 11-3, 14.2.4.2.1, 14.2.4.2.2 and individual listings in 16.2.6.2.1 will be listed as per the above formats with connecting the mean values between the pre- and post-dialysis results within the same day but without connecting the values between days.

- y-axis: <Bun> (unit)
- X-axis: Day

Figures in Appendices 16.2.6.1.1 and 16.2.6.1.2 will be in the following format:

Appendix 16.2.6.1.1
Individual Plasma APC-PCI Concentrations Versus Time Profiles Following Administration of 1.5 µg/kg E-WE Thrombin (Linear Scale) for <Subject #>



Notes for Generating the Actual Individual Figure:

- y-axis: Plasma APC-PCI Concentration (unit)
- X-axis: Hours From Start of Dose

Figure Legend: Use the Short Description as presented in Section 5.

Program: /CAXXXXX/sas_prg/pksas/indgraph-all.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_indgraph.sas DDMMMYYYY HH:MM

10.3 Section 14 Summary Tables Shells

Table 14.1.1 Summary of Disposition Safety Population)

	Dose Level of E-WE Thrombin			
Disposition	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)	Overall
Dosed	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Completed	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Discontinued	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Reason 1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Reason 2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)

Program: /CAXXXXX/sas_prg/stsas/tab PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.2 Demographic Summary (Safety Population)

Trait	Category/ Statistics	Dose Level of E-WE Thrombin 1.5 µg/kg	Dose Level of E-WE Thrombin 3.0 µg/kg	Placebo (Pooled)	Overall
Sex	Male	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Female	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Race	Asian	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Black or African American	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	White	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Ethnicity	Hispanic or Latino	X (XX%)	X (XX%)	X (XX%)	X (XX%)
	Not Hispanic or Latino	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Age* (yrs)	n	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X
	Maximum	XX	XX	XX	XX
Weight (kg)	n	X	X	X	X
	Mean	XX.X	XX.X	XX.X	XX.X
	SD	X.XX	X.XX	X.XX	X.XX
	Minimum	XX	XX	XX	XX
	Median	XX.X	XX.X	XX.X	XX.X
	Maximum	XX	XX	XX	XX

Programmer Note: This is just a mock table shell. Please use the race categories listed in the CRF. Please also include Height (cm) and BMI (kg/m2).

Note: *Age is calculated at the time of informed consent.

Program: /CAXXXXX/sas_prg/stsas/tab PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.1.1.1 through 14.2.1.1.3 will be in the following format:

Table 14.2.1.1.1 Plasma APC-PCI Concentrations (unit) Following Administration of 1.5 µg/kg E-WE Thrombin – Day 1 (PD Population)

Subject	Sample Times (hr)								
Number	Predose	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
n	XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SD	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%	.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum	XX	XX	XX	XX	XX	XX	XX	XX	XX
Median	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Maximum	XX	XX	XX	XX	XX	XX	XX	XX	XX

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of <X> ng/mL are treated as 0 before the first quantifiable concentration and as missing elsewhere.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

- Please use CPConc1 template
- Per study design needs, the following changes are made to this table relative to Celerion standard: columns <Treatment Sequence> and <Study Period> will be removed;
- Concentrations will be presented to the same precision as in the bio data;
- Summary statistics presentation with respect to the precision of the bio data or clinical laboratory data: n = integer; Mean and Median +1; SD and SEM +2, Minimum and Maximum +0, CV% to 1 decimal;
- PK Time points are: predose (hour 0) and 0.167, 0.5, 1, 2, 4, 6, and 24 hours post E-WE Thrombin bolus dose;
- For Table 14.2.1.1.3 there will be no summary statistics.

Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables-sig.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/adam_conc.sas DDMMMYYYY HH:MM

Tables 14.2.2.1 will be in the following format:

Table 14.2.2.1 Summary of Clotting in Dialysis Venous Chamber Days -7 to 3 (PD Population)

		1.5 µg/kg E-WE Thrombin							3.0 µg/kg E-WE Thrombin							Placebo (Pooled)						
		Category*							Category*							Category*						
Day	Time Point	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Day -7	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -5	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -2	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 1	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 3	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: *Category:1 = No detectable clotting
2 = Presence of fibrinous ring or minimum clot affecting less than 5% of chamber space,
3 = Clot formation (affecting more than 5% of but less than 25% of chamber space),
4 = Clot formation (affecting more than 25% of but less than 50% of chamber space),
5 = Clot formation (affecting more than 50% of but less than 75% of chamber space),
6 = Clot formation (affecting more than 75% of chamber space),
7 = Occluded (also assess the category of clot that caused occlusion)
HD: hemodialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.3.1 will be in the following format:

Table 14.2.3.1 Summary of Clotting in the Dialysis Filter (Safety Population)

		1.5 µg/kg E-WE Thrombin						3.0 µg/kg E-WE Thrombin						Placebo (Pooled)					
		Category*						Category*						Category*					
Day	Time Point	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
Day -7	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -5	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day -2	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 1	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Day 3	Post HD	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: *Category:1 = No clotting, clean filter or few blood streaks (affecting less than 5% of the fibers seen at the surface of dialyzer),
2 = Blood streaks affecting more than 5% but less than 25 % of the fibers seen at the surface of the dialyzer,
3 = Blood streaks affecting more than 25% but less than 50 % of the fibers seen at the surface of the dialyzer,
4 = Blood streaks affecting more than 50% but less than 75 % of the fibers seen at the surface of the dialyzer,
5 = Blood streaks affecting more than 75% of the fibers seen at the surface if the dialyzer,
6 = Occluded (also assess the category of streaking at the time of occlusion)
HD: hemodialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.4.1.1 through 14.2.4.1.3 will have the following format:

Table 14.2.4.1.1 Individual and Mean Difference between Pre- and Post-dialysis BUN Values (unit) and URR – Days -7 to 3 – 1.5 µg/kg E-WE Thrombin on Day 1 (PD Population)

<continue with HD Days -5, -2, 1 and 3>

Subject Number	Day	Pre-dialysis (unit)	Post-dialysis (unit)	Difference (unit)	URR (%)
X	-7	XXX	X.XX	XXX	XXX
X	-7	XX.X	X.XX	XXX	XXX
X	-7	XX.X	X.XX	XXX	XXX
X	-7	X.XX	X.XX	XXX	XXX
X	-7	XXX	X.XX	XXX	XXX
n		XX	XX	XX	XX
Mean		XXX.X	XXX.X	X.XXX	XXX.X
SD		XX.XX	XX.XX	XX.XX	XX.XX
CV%		XX.X	XX.X	XX.X	XX.X
SEM		XX.XX	XX.XX	XX.XX	XX.XX
Minimum		XX.X	XX.X	X.XX	XXX
Median		XX.XX	XX.XX	X.XXX	XXX.X
Maximum		XXX	XXX	X.XX	XXX

1.5 µg/kg: On Day 1, 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg

Difference = Pre-dialysis - Post-dialysis

footnotes:
Difference = Pre-dialysis - Post-dialysis
Single IV dose of 1.5 µg/kg E-WE Thrombin was administered on Day 1
URR = (1-(post-dialysis BUN/ pre-dialysis BUN))*100

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.5.1.1 through 14.2.5.1.3 will have the following format:

Table 14.2.4.1.1 Individual and Mean Kt/V Values (unit) – 1.5 µg/kg E-WE Thrombin on Day 1 (PD Population)

<continue with HD Days -5, -2, 1 and 3>

Subject Number	Day	R (unit)	t (unit)	UF (unit)	Wt (%)	Kt/V (unit)
X	-7	XXX	X.XX	XXX	XXX	XXX
X	-7	XX.X	X.XX	XXX	XXX	XXX
X	-7	XX.X	X.XX	XXX	XXX	XXX
X	-7	X.XX	X.XX	XXX	XXX	XXX
X	-7	XXX	X.XX	XXX	XXX	XXX
n		XX	XX	XX	XX	XX	XX
Mean		XXX.X	XXX.X	XXX.X	X.XXX	XXX.X	XXX.X
SD		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%		XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM		XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum		XX.X	XX.X	XX.X	X.XX	XXX	XXX
Median		XX.XX	XX.XX	XX.XX	X.XXX	XXX.X	XXX.X
Maximum		XXX	XXX	XXX	X.XX	XXX	XXX

1.5 µg/kg: On Day 1, 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg

Footnotes:

Single IV dose of 1.5 µg/kg E-WE Thrombin was administered on Day 1
R = post-dialysis BUN/pre-dialysis BUN))*100
t = Time of HD
UF = Pre-dialysis Weight – Post-dialysis Weight
Wt = Post-dialysis weight of patient

$$\text{Kt/V} = -\ln(\text{R} - (0.008 \times \text{t})) + (4 - (3.5 \times \text{R})) \times \frac{\text{UF}}{\text{Wt}}$$

Program: /CAXXXXX/sas_prg/pksas/xxxxxxxx.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/xxxxxxxxx.sas DDMMMYYYY HH:MM

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Treatment - Number of Subjects Reporting the Event
(% of Subjects Dosed) (Safety Population)

	Dose Level of E-WE Thrombin			
Adverse Event*	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)	Overall
Number of Subjects Dosed	XX (XX%)	XX (XXX%)	XX (XX%)	XX (XXX%)
Number of Subjects With TEAEs^	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without TEAEs^	XX (XX%)	XX (XXX%)	XX (XX%)	XX (XXX%)
Nervous system disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Dizziness	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Headache	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Presyncope	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Respiratory, thoracic and mediastinal disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Dry throat	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Oropharyngeal pain	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sinus congestion	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sneezing	X (XX%)	X (XX%)	X (XX%)	X (XX%)
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Fatigue	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Thirst	X (XX%)	X (XX%)	X (XX%)	X (XX%)

Note: *Adverse events are classified according to MedDRA Version 21.1. ^ = Treatment-emergent adverse events
If a subject has 2 or more clinical adverse events, the subject is counted only once within a category. The same subject may appear in different categories.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Treatment - Number of Adverse Events (% of Total Adverse Events) (Safety Population)

	Dose Level of E-WE Thrombin			
Adverse Event*	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)	Overall
Number of TEAEs	X (100%)	X (100%)	X (XX%)	X (XX%)
Nervous system disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Dizziness	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Headache	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Presyncope	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Respiratory, thoracic and mediastinal disorders	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Dry throat	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Oropharyngeal pain	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sinus congestion	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Sneezing	X (XX%)	X (XX%)	X (XX%)	X (XX%)
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Fatigue	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Thirst	X (XX%)	X (XX%)	X (XX%)	X (XX%)

Note: *Adverse events are classified according to MedDRA Version 21.1. ^ = Treatment-emergent adverse events

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.3 Treatment-Emergent Adverse Event Frequency by Treatment, Severity, and Relationship to Study Drug - Number of Adverse Events (Safety Population)

Adverse Event*	Cohort/ Treatment	Number of Subjects With TEAEs	Number of TEAEs	Severity				Relationship to Study Drug				
				Grade 1	Grade 2	Grade 3	Grade 4	Unrelated	Unlikely	Possibly	Probably	Likely
Dizziness	1/A	X	X	X	X	X	X	X	X	X	X	X
	X/X	X	X	X	X	X	X	X	X	X	X	X
Dry eye	X/X	X	X	X	X	X	X	X	X	X	X	X
Dry mouth	X/X	X	X	X	X	X	X	X	X	X	X	X
Dry throat	X/X	X	X	X	X	X	X	X	X	X	X	X
Ear pain	X/X	X	X	X	X	X	X	X	X	X	X	X
Fatigue	X/X	X	X	X	X	X	X	X	X	X	X	X
Headache	X/X	X	X	X	X	X	X	X	X	X	X	X
Dizziness	X/X	X	X	X	X	X	X	X	X	X	X	X
Hyperhidrosis	X/X	X	X	X	X	X	X	X	X	X	X	X
Laceration	X/X	X	X	X	X	X	X	X	X	X	X	X
Limb crushing injury	X/X	X	X	X	X	X	X	X	X	X	X	X
Muscle twitching	X/X	X	X	X	X	X	X	X	X	X	X	X
1.5 µg/kg E-WE Thrombin		X	X	X	X	X	X	X	X	X	X	X
3.0 µg/kg E-WE Thrombin		X	X	X	X	X	X	X	X	X	X	X
Placebo (Pooled)		X	X	X	X	X	X	X	X	X	X	X
Overall		XX	XX	X	X	X	X	X	X	X	X	X

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

*Adverse events are classified according to MedDRA Version 21.1. TEAE = Treatment-emergent adverse events
If a subject experience the same adverse event (AE) at more than one level of severity during a treatment, each AE is counted separately. If a subject experience the same AE at more than one level of drug relationship during a treatment, each AE is counted separately.
Severity: Grade 1 = Mild; Grade 2 = Moderate; Grade 3 = Severe; Grade 4 = Potentially life-threatening

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.4.1 to 14.3.4.3 will have the following format:

Table 14.3.4.1 Out-of-Range Values and Clinically Significant Results - Serum Chemistry (Safety Population)

Subject Number	Cohort/ Treatment	Age#/ Sex	Study Visit	Hour	Date	Time	Parameter1 <Range> (Unit)	Parameter2 <Range> (Unit)	Parameter3 <Range> (Unit)	Parameter4 <Range> (Unit)	Parameter5 <Range> (Unit)
X	1/A	XX/X	Screen	.	DDMMMYYYY	HH:MM:SS	XX H +				XX L
			Day X	XX	DDMMMYYYY	HH:MM:SS	XX L	XX L	XX H	XX L	
			Unscheduled		DDMMMYYYY	HH:MM:SS				XX	

Programmer Notes: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early termination chronologically with other scheduled assessments.

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
#Age is calculated at the time of first dosing. F = Female; M = Male
H = Above reference range, L = Below reference range
PI Interpretation: + = Clinically significant

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.5.1 and 14.3.5.3 will be in the following format:

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline - Serum Chemistry (Safety Population)

Laboratory Test (unit)	Reference Range	Time Point	Statistic	Dose Level of E-WE Thrombin 1.5 µg/kg	Dose Level of E-WE Thrombin 3.0 µg/kg	Dose Level of E-WE Thrombin Placebo (Pooled)	Change from Baseline* 1.5 µg/kg	Change from Baseline* 3.0 µg/kg	Change from Baseline* Placebo (Pooled)
XXXXXXXXX (unit)	X.X-XX.X#	Screen	n	XX	XX	XX			
			Mean	X.XX	X.XX	X.XX			
			SD	X.XXX	X.XXX	X.XXX			
			Minimum	X.XX	X.XX	X.XX			
			Median	X.X	X.X	X.X			
			Maximum	XX.X	XX.X	XX.X			
		Baseline*	n	XX	XX	XX			
			Mean	X.XX	X.XX	X.XX			
			SD	X.XXX	X.XXX	X.XXX			
			Minimum	X.XX	X.XX	X.XX			
			Median	X.X	X.X	X.X			
			Maximum	XX.X	XX.X	XX.X			
		Day X, Hour X.XX	n	XX	XX	XX	XX	XX	XX
			Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
			Minimum	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Median	X.X	X.X	X.X	X.X	X.X	X.X
			Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<include all timepoints>

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
* Baseline is defined as the result closest and prior to dose on Day 1.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.5.2 and 14.3.5.4 will be in the following format:

Table 14.3.5.2 Clinical Laboratory Shift From Baseline - Serum Chemistry (Safety Population)

Laboratory Test (unit)	Treatment	Time Point	Baseline* L			Baseline* N			Baseline* H		
			L	N	H	L	N	H	L	N	H
XXXXXXX (unit)	XXX <units>	Day X, Hour X.XX	X	XX	X	X	XX	X	X	XX	X

Note: 1.5 µg/kg: 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
3.0 µg/kg: 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
Placebo = pooled placebo
N = Within Normal Range, L = Below Normal Range, H = Above Normal Range
* Baseline is defined as the result closest and prior to dose on Day 1.

Program: /AAXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMYYYY HH:MM

Table 14.3.5.5 Clinical Laboratory Summary – Coagulation and Platelet Count (Safety Population)

Laboratory Test (unit)	Reference Range	Time Point	Statistic	1.5 µg/kg E-WE Thrombin Pre-HD	1.5 µg/kg E-WE Thrombin Post-HD	1.5 µg/kg E-WE Thrombin Fold Change	3.0 µg/kg E-WE Thrombin Pre-HD	3.0 µg/kg E-WE Thrombin Post-HD	3.0 µg/kg E-WE Thrombin Fold Change	Placebo (Pooled) Pre-HD	Placebo (Pooled) Post-HD	Placebo (Pooled) Fold Change
XXXXXXXXX (unit)	X.X-XX.X#	Screen	n	XX			XX			XX		
			Mean	X.XX			X.XX			X.XX		
			SD	X.XXX			X.XXX			X.XXX		
			Minimum	X.XX			X.XX			X.XX		
			Median	X.X			X.X			X.X		
			Maximum	XX.X			XX.X			XX.X		
		Day -8	n	XX			XX			XX		
			Mean	X.XX			X.XX			X.XX		
			SD	X.XXX			X.XXX			X.XXX		
			Minimum	X.XX			X.XX			X.XX		
			Median	X.X			X.X			X.X		
			Maximum	XX.X			XX.X			XX.X		
		Day X	n	XX	XX	XX	XX	XX	XX	XX	XX	XX
			Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
			Minimum	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
			Median	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X	X.X
			Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

<include all remaining HD days>

Programmer note: This table will include aPTT, PT, INR, PT/INR, fibrinogen, TT from coagulation and platelet count form hematology. for PT, INR and PT/INR, the pre-dialysis value will be the baseline value for that day and the "change from baseline" will be the fold change from baseline "ie. Post-dialysis / Pre-dialysis.

Note: # = Lowest of the lower ranges and highest of the higher ranges are used. Refer to Appendix 16.1.10.1 for the breakdown.
Fold change = Post-dialysis / Pre-dialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.6 Vital Sign Summary and Change from Baseline (Safety Population)

			Dose Level of E-WE Thrombin			Change from Baseline*		
Vital Sign (unit)	Time Point	Statistic	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)
XXXXXXXXX (unit)	Screen	n	XX	XX	XX			
		Mean	X.XX	X.XX	X.XX			
		SD	X.XXX	X.XXX	X.XXX			
		Minimum	X.XX	X.XX	X.XX			
		Median	X.X	X.X	X.X			
		Maximum	XX.X	XX.X	XX.X			
	<Also include Days -8, -7, -5 and -2>							
	Baseline*	n	XX	XX	XX			
		Mean	X.XX	X.XX	X.XX			
		SD	X.XXX	X.XXX	X.XXX			
		Minimum	X.XX	X.XX	X.XX			
		Median	X.X	X.X	X.X			
		Maximum	XX.X	XX.X	XX.X			
	Day X, Hour X.XX	n	XX	XX	XX	XX	XX	XX
		Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

Note: * Baseline is defined as the result closest and prior to the dose on Day 1.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.7 Summarization of Weight (Safety Population)

		Dose Level of E-WE Thrombin		
Time Point	Statistic	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)
Screen	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X
Day -8, Check-in	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X
Day -7, Before HD	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X

<Also include before and after HD timepoints on Days -7, -5, -2, 1 and 3>

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.8 12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

			Dose Level of E-WE Thrombin			Change from Baseline*		
Measurement(unit)	Time Point	Statistic	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)
XXXXXXXXX (unit)	Screen	n	XX	XX	XX			
		Mean	X.XX	X.XX	X.XX			
		SD	X.XXX	X.XXX	X.XXX			
		Minimum	X.XX	X.XX	X.XX			
		Median	X.X	X.X	X.X			
		Maximum	XX.X	XX.X	XX.X			
	Day -8 Check-in*	n	XX	XX	XX			
		Mean	X.XX	X.XX	X.XX			
		SD	X.XXX	X.XXX	X.XXX			
		Minimum	X.XX	X.XX	X.XX			
		Median	X.X	X.X	X.X			
		Maximum	XX.X	XX.X	XX.X			
	Day 1, Hour X.XX	n	XX	XX	XX	XX	XX	XX
		Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	Day 3, Hour X.XX	n	XX	XX	XX	XX	XX	XX
		Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
		Minimum	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
		Median	X.X	X.X	X.X	X.X	X.X	X.X
		Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

Note: * Baseline is Day -8 Check-in.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.9 Summarization of Bleeding Time (Safety Population)

		Dose Level of E-WE Thrombin		
Time Point	Statistic	1.5 µg/kg	3.0 µg/kg	Placebo (Pooled)
Day -7	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X
Day -5	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X
Day -2	n	XX	XX	XX
	Mean	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX
	Minimum	X.XX	X.XX	X.XX
	Median	X.X	X.X	X.X
	Maximum	XX.X	XX.X	XX.X

<Also include Days 1 and 3>

Programmer note: Bleeding time is recorded on the Dialyzer Assessment CRF page under item #4 as length of time of pressure on puncture site.

Note: Bleeding time in minutes was assessed immediately after the end of hemodialysis and removal of the needles from the fistula or graft.

Program: /AAXXXXX/ECR/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

11. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final CSR. These listings will be generated off of the Celerion SDTM datasets (SDTM Tabulation Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2). All listings will be presented in Courier New font size 9.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Sex	Age Category	Reference Range	Unit
Serum Chemistry	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
Hematology	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units

<similar for remaining Laboratory Groups and Test Names>

Programmer note: Please add a column for site ID if multiple sites are used.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.1 Study Completion/Early Termination (Safety Population)

Subject Number	Cohort/ Treatment	Completed Study?	Date	Date of Last Contact	Reason for Discontinuation	Comments
X	1/A	Yes	DDMMMYYYY	DDMMMYYYY		
X	1/A	Yes	DDMMMYYYY	DDMMMYYYY		
X	1/P	Yes	DDMMMYYYY	DDMMMYYYY		
X	1/A	Yes	DDMMMYYYY	DDMMMYYYY		
X	1/A	No	DDMMMYYYY	DDMMMYYYY	XXXXXXXXXXXXXX	XXXXXXXX
X	1/P	Yes	DDMMMYYYY	DDMMMYYYY		

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.1 Demographics (Safety Population)

Subject Number	Cohort/ Treatment	Date of Birth	Age* (yrs)	Gender	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	Informed Consent Date
X	1/A	MMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY
X	1/A	MMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY
X	1/P	MMMYYYY	XX	AAAAAA	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	DDMMMYYYY

Note: *Age is calculated from the date of informed consent.
Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2 Physical Examination (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Study Time	Date	Body System	Result	Abnormality	Clinical Significance
X	1/A	Screen		DDMMMYYYY	1. General Appearance	Abnormal	XXXXXXXXXXXXXXXXXXXX	NCS

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Medical and Surgical Histories (Safety Population)

Subject Number	Cohort/ Treatment	Seq #	Description	Date of Diagnosis/Surgery Start	End	Ongoing?
X	1/A	X	XXXXXX XXXXX XXXXXXX	MMYYYY		Yes
		X	XXXXXXXXX	MMMYYYY	MMMYYYY	No
		X	XXXXXXXX XXXXX XXXXXX	MMMYYYY	MMMYYYY	No

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Alcohol Screen (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Visit Date	Type of Sample	Actual Time	Result
X	1/A	Screen	DDMMMYYYY	Breath	HH:MM	Negative

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.5 Saliva Drug Screen (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Visit Date	Actual Time	Result	If Positive, list all that were positive:
X	1/A	Screen	DDMMMYYYY	HH:MM	Negative	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.6 Tobacco Use (Safety Population)

Subject Number	Cohort/ Treatment	Visit Date	Tobacco Use	Start Date	Stop Date
X	1/A	DDMMMYYYY	Never Used		
X	1/A	DDMMMYYYY	Former User	DDMMMYYYY	DDMMMYYYY
X	1/P	DDMMMYYYY	Current User	DDMMMYYYY	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.1 Subject Eligibility at Screening (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Visit Date	Did subject meet all eligibility criteria?	Criterion Not Met	Specify
X	1/A	Screen	DDMMMYYYY	Yes		
X	1/A	Screen	DDMMMYYYY	Yes		
X	1/P	Screen	DDMMMYYYY	No	EXCLUSION X	XXXXXXXXXXXXXX XXXX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Subject Eligibility at Check-In (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Date	Does subject continue to meet criteria since Screening?	If No, specify
X	1/A	Day -8 Check-In	DDMMMYYYY	Yes	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3 Test Compound Administration (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Study Time	Date	Dose Administered?	Bolus Administration Time	Dosing Start Time	Dosing End Time	Route	Form	Frequency
X	1/A	Day 1	Hour 0	DDMMMYYYY	Yes	HH:MM:SS	HH:MM:SS	HH:MM:SS	IV Infusion	Injection	Once

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4 Blood Draw Times for E-WE Thrombin PD (APC-PCI) (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Comments
X	1/A	X	Predose	DDMMMYYYY	XX:XX	XXXXXXXXXX
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	XXXXXXXXX
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
		X	XX.XX	DDMMMYYYY	XX:XX	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.5 Blood Draw Times for Protein C (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Comments
X	1/A	-7	Start HD	DDMMMYYYY	HH:MM	XXXXXXXXXX
			End HD		HH:MM	
		-5	Start HD	DDMMMYYYY	XX:XX	
			End HD		HH:MM	
		-2	Start HD	DDMMMYYYY	XX:XX	
			End HD		HH:MM	
		1	Predose	DDMMMYYYY	XX:XX	XXXXXXXXX
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
			XX.XX	DDMMMYYYY	XX:XX	
		2	XX.XX	DDMMMYYYY	XX:XX	
		3	Start HD	DDMMMYYYY	XX:XX	
			End HD		HH:MM	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.6 Blood Draw Times for Immunogenicity (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Comments
X	1/A	1	Predose	DDMMMYYYY	HH:MM	XXXXXXXXXX
		14	Follow-up	DDMMMYYYY	HH:MM	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.7 Blood Draw Times for Dialysate Analysis for Kt/V and URR (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Comments
X	1/A	-7	Pre HD	DDMMMYYYY	HH:MM	XXXXXXXXXX
			End of HD	DDMMMYYYY	HH:MM	
		-5	Pre HD	DDMMMYYYY	HH:MM	
			End of HD	DDMMMYYYY	HH:MM	
		-2	Pre HD	DDMMMYYYY	HH:MM	
			End of HD	DDMMMYYYY	HH:MM	
		1	Pre HD	DDMMMYYYY	HH:MM	
			End of HD	DDMMMYYYY	HH:MM	
		3	Pre HD	DDMMMYYYY	HH:MM	
			End of HD	DDMMMYYYY	HH:MM	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
HD = Hemodialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.8 Dialysate Collection (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Comments
X	1/A	-7	30 min after start of HD	DDMMMYYYY	HH:MM	XXXXXXXXXX
			3 hours after start of HD	DDMMMYYYY	HH:MM	
		-5	30 min after start of HD	DDMMMYYYY	HH:MM	
			3 hours after start of HD	DDMMMYYYY	HH:MM	
		-2	30 min after start of HD	DDMMMYYYY	HH:MM	
			3 hours after start of HD	DDMMMYYYY	HH:MM	
		1	30 min after start of HD	DDMMMYYYY	HH:MM	
			3 hours after start of HD	DDMMMYYYY	HH:MM	
		3	30 min after start of HD	DDMMMYYYY	HH:MM	
			3 hours after start of HD	DDMMMYYYY	HH:MM	

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
HD = Hemodialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.9.1 Dialyzer Assessment (I of V) – Hemodialysis Start and End Times(Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Hemodialysis Start	Hemodialysis End	Interrupted Prematurely?	Reason for Interruption	Specify
X	1/A	X	HH:MM	HH:MM	Yes	XXXXXXXXXXXXX	XXXXXXXXX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.9.2 Dialyzer Assessment (II of V) - Circuit Arterial and Venous Pressure and Blood Flow Rate(Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Time Relative To Dialysis	Arterial Pressure Time	Arterial Pressure mmHg	Venous Pressure Time	Venous Pressure mmHg	Blood Flow Rate mL/min	Time to Hemostasis Time	Time to Hemostasis Length (min)	Dialysis/ Venous Chamber Photographed?	Dialysis Filter/ Venous Chamber Collected?	Ultra Filtration Volume (mL)
X	1/A	X	0 Hour	HH:MM	XX	HH:MM	XX	XX	HH:MM	XX	Yes	Yes	XXX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.9.3 Dialyzer Assessment (III of V) - Number and Volume of Saline Flushes(Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Saline Flush Number	Time of Flush	Volume (mL)	Total Volume of Flushes (mL)	Total Number of Flushes
X	1/A	X	1	HH:MM	XX	XXX	XX
			2	HH:MM	XX		
			3	HH:MM	XX		
			4	HH:MM	XX		
			5	HH:MM	XX		
			6	HH:MM	XX		

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.9.4 Dialyzer Assessment (IV of V) – Clotting in Dialysis Venous Chamber (Safety Population)

			Venous Chamber #1								Venous Chamber #2 (if needed)							
				Category*								Category*						
Subject Number	Cohort/ Treatment	Study Day	Time	1	2	3	4	5	6	7	Time	1	2	3	4	5	6	7
X	1/A	X	HH:MM	X	X	X	X	X	X	X	HH:MM	X	X	X	X	X	X	X

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
*Category:1 = No detectable clotting, 2 = Presence of fibrinous ring or minimum clot affecting less than 5% of chamber space,
3 = Clot formation (affecting more than 5% of but less than 25% of chamber space),
4 = Clot formation (affecting more than 25% of but less than 50% of chamber space),
5 = Clot formation (affecting more than 50% of but less than 75% of chamber space),
6 = Clot formation (affecting more than 75% of chamber space),
7 = Occluded (also assess the category of clot that caused occlusion)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.9.5 Dialyzer Assessment (V of V) – Clotting in Dialysis Filter (Safety Population)

			End of Dialysis (or premature interruption)													
			Dialysis Filter #1							Dialysis Filter #2 (if needed)						
				Category*							Category*					
Subject Number	Cohort/ Treatment	Study Day	Time	1	2	3	4	5	6	Time	1	2	3	4	5	6
X	1/A	X	HH:MM	X	X	X	X	X	X	HH:MM	X	X	X	X	X	X

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

*Category: 1 = No clotting, clean filter or few blood streaks (affecting less than 5% of the fibers seen at the surface of dialyzer),
2 = Blood streaks affecting more than 5% but less than 25 % of the fibers seen at the surface of the dialyzer,
3 = Blood streaks affecting more than 25% but less than 50 % of the fibers seen at the surface of the dialyzer,
4 = Blood streaks affecting more than 50% but less than 75 % of the fibers seen at the surface of the dialyzer,
5 = Blood streaks affecting more than 75% of the fibers seen at the surface if the dialyzer,
6 = Occluded (also assess the category of streaking at the time of occlusion)

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.10 Non-Study Procedures (Safety Population)

Subject Number	Cohort/ Treatment	Procedure	Assessment Date	Procedure Date	Procedure Time	Due to Medical History, seq#	Due to AE, AE page#	Overall Procedure Interpretation	Procedure Findings/Comments
X	1/A	None							
		XXXXXXXXXXXX	DDMMMYYYY	DDMMMYYYY	HH:MM	XXXXXXX	XX	XXXXXXXXXXXXXXXX	XXXXXXXXXXXXXXXXXXX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.11 Prior and On-Study Concomitant Medications (Safety Population)

Subject Number	Cohort/ Treatment	Any Med?	Medication (WHO* Term)	Dosage	Form	Route	Start Date	Start Time	Stop Date	Stop Time	Fre-quency	Indication	Con-tinuing?	Prior to Study?	If Due to AE, AE Page#
X	1/A	No	None												
X	1/A	Yes	ACETAMINOPHEN (ACETAMINOPHEN)	620 mg	XXX	Oral	DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	Once	Toothache	No	X	XX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
*Concomitant medications are coded with World Health Organization (WHO) Drug Dictionary Version September 2018, B3.
Med = Medication

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1.1 Adverse Events (I of II) (Safety Population)

Subject Number	Cohort/ Treatment	TE?^	Adverse Event*	Preferred Term	Time From Last Dose (DD:HH:MM)	Onset Date	Onset Time	Resolved Date	Resolved Time	Duration (DD:HH:MM)
X	1/A	None								
X	1/A	Yes	XXXXXXXXXXXX	XXXXXXXXX XXXXXXX	XX:XX:XX	DDMMMYYYY	XX:XX	DDMMMYYYY	XX:XX	XX:XX:XX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
*Adverse events are classified according to MedDRA Version 21.1.
^TE = Treatment-emergent

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1.2 Adverse Events (II of II) (Safety Population)

Subject Number	Cohort/ Treatment	TE?^	Adverse Event	Onset Date	Onset Time	Severity/ Intensity	Serious	Outcome	Relationship to Study Drug	Action
X	1/A	None								
X	1/A	Yes	XXXXXXXXXXXXXXXXXX	DDMMMYYYY	XX:XX	Grade 1 Mild	Not serious	Resolved	XXXXXXXXXXXXXXX	XXXXXXXXX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
^TE = Treatment-emergent

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.2 Adverse Event Preferred Term Classification (Safety Population)

Subject Number	Cohort/ Treatment	TE?^	Adverse Event*	Preferred Term	System Organ Class	Onset Date	Onset Time
X	1/A	Yes	XXXXXXX XXXXX XXXX XXXXXX	XXXXXXXXX XXXXXXX	XXXXXXXXXXXXXXXXXXXX	DDMMMYYYY	XX:XX

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
*Adverse events are classified according to MedDRA Version 21.1.
^TE = Treatment-emergent

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendices 16.2.8.1.1, 16.2.8.1.2, 16.2.8.1.4 and 16.2.8.1.5 will have the following format.

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)

Subject Number	Cohort/ Treatment	Age#/ Sex	Study Visit		Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)	Parameter6 < Range> (Unit)
X	1/A	XX/X	Screen	DDMMMYYYY	XX H	XX	XX	XX	XX H	XX
			X	DDMMMYYYY	XX L +	XX L	XX	XX L	XX	XX

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Programmer Note: Please adjust layout based on what is actually in the database if necessary.

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
#Age is calculated from the date of first dosing. F = Female; M = Male
H = Above reference range, L = Below reference range
PI interpretation: + = Clinically Significant

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.3 Clinical Laboratory Report – Coagulation and Platelet Count (Safety Population)

Subject Number	Cohort/ Treatment	Age#/ Sex	Study Visit	Study Hour	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)	Parameter6 < Range> (Unit)
X	1/A	XX/X	Screen		DDMMMYYYY	XX H	XX	XX	XX	XX H	XX
			X	XX	DDMMMYYYY	XX L +	XX L	XX	XX L	XX	XX

Programmer Note: A study hour column is included for coagulation and platelet count due to more frequent assessments. Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Programmer Note: Please adjust layout based on what is actually in the database if necessary. Remove Other if no other tests. This listing includes PT/INR, fibrinogen, and TT from coagulation and platelet count from hematology.

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
#Age is calculated from the date of first dosing. F = Female; M = Male
H = Above reference range, L = Below reference range
PI interpretation: + = Clinically Significant

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.1.6 Clinical Laboratory Report - Comments (Safety Population)

Programmer Note: Remove this listing if comments are not collected.

Appendix 16.2.8.2 Vital Signs (Safety Population)

Subject Number	Study Visit	Hour	Date	Time	Position	Blood Pressure (mmHg) Systolic/Diastolic	Heart Rate (bpm)	Respiration (bpm)	Temperature (°C)	Weight (kg)
X	Screen	.	DDMMMYYYY	XX:XX	Seated	XXX/ XX	XX	XX	XX.X	XX.X
	Day -8	Check-In	DDMMMYYYY	XX:XX	XXXXXXXX	XXX/ XX	XX	XX	XX.X	XX.X
	Day -7	Pre HD	DDMMMYYYY	XX:XX	XXXXXX	XXX/ XX	XX	XX	XX.X	XX.X
	Day -7	Post HD	DDMMMYYYY	XX:XX						XX.X

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Programmer Note: Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.3 12-Lead Electrocardiogram (Safety Population)

Subject Number	Cohort/ Treatment	Study Visit	Hour	Visit Date	Time	Result	Heart Rate (bpm)	PR (ms)	QRS (ms)	QT (ms)	QTcF* (ms)	Comments
X	1/A	Screen	.	DDMMMYYYY	XX:XX	Normal	XX	XXX	XX	XXX	XXX^#	XXXXXXXXX
		Day X	XX.X	DDMMMYYYY	XX:XX	Normal	XX	XXX	XX	XXX	XXX	
		Day X	XX.X	DDMMMYYYY	XX:XX	Normal	XX	XXX	XX	XXX	XXX	

Programmer Note: Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Note: QTcF* = QT corrected for heart rate using Fridericia's correction.
Abnormal, NCS = Abnormal, Not clinically significant
^ = QTcF is > 450 ms
# = QTcF change from baseline is > 30 ms
Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.4 Vascular Access Site Reaction Assessment (Safety Population)

Subject Number	Cohort/ Treatment	Study Day	Study Hour	Collection Date	Actual Time	Was a Reaction Observed?	If yes, Grade (1,2 or 3)
X	1/A	1	Predose	DDMMMYYYY	HH:MM	XXX	X
			4 Hours postdose	DDMMMYYYY	HH:MM	XXX	X
		3	Start of HD	DDMMMYYYY	HH:MM	XX	
			20 min Post HD	DDMMMYYYY	HH:MM	XXX	X

Note: Treatment: A = 0.5 µg/kg bolus dose of E-WE Thrombin followed by a 0.25 µg/kg/hour continuous infusion over 4 hours for a total dose of 1.5 µg/kg
B = 1.0 µg/kg bolus dose of E-WE Thrombin followed by a 0.5 µg/kg/hour continuous infusion over 4 hours for a total dose of 3.0 µg/kg
P = Placebo
HD = Hemodialysis

Program: /AAXXXXX/ECR/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM