

A Phase 3 **S**tudy of the Safety and Efficacy of **Co**agulation Factor VIIa (Recombinant) for the **P**revention of **E**xcessive Bleeding in Patients with Congenital **H**emophilia A or B with **I**nhibitors to Factor VIII or IX Undergoing Elective **M**ajor Surgical Procedures

Statistical Analysis Plan

Study ID: F7TG2202

Version 1.0
Date: May 24, 2023

SIGNATURE PAGE

The undersigned hereby jointly declare that they have examined the Statistical Analysis Plan (SAP) and agree to its form and content. Furthermore, they confirm that the SAP outlined sufficiently provides details to the intended analysis for the study as provided in protocol F7TG2202.

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition or explanation
ADaM	Analysis data model
AE	Adverse Event
AESI	Adverse Event of Special Interest
aPTT	Activated Partial Thromboplastin Time
AT III	Antithrombin III
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BU	Bethesda units
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CM	Concomitant medication
COVID-19	Coronavirus disease 2019 (SARS-CoV-2)
CSR	Clinical Study Report
D5	Day 5
D15	Day 15
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EoS	End of Study
F 1+2	Prothrombin Fragment 1+2
FAS	Full-Analysis set
FDA	Food and Drug Administration
FIX	Factor IX
FVIII	Factor VIII
h	Hours
Hb	Hemoglobin
Hct	Hematocrit
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	Identification number
IMP	Investigational Medicinal Product
IO	Intra-operative
IRS	Interactive Response System
ITI	Immune tolerance induction
IV	Intravenous
CCI	Coagulation Factor VIIa (Recombinant)
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
PCR	Polymerase chain reaction
PD	Protocol deviation
PDF	Portable document format
PDG	Protocol deviation guidance

PO	Post-operative
PP	Per Protocol
PT	Preferred term
PT	Prothrombin time
RBC	Red blood cell
rtf	Rich text format
SAE	Serious Adverse Event
SAF	Safety population
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
sBLA	Supplemental Biologics License Application
SBP	Systolic Blood Pressure
SDTM	Study Data Tabulation Model
SI	Standard international
SOC	System Organ Class
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
TEAESI	Treatment Emergent Adverse Event of Special Interest
TLF	Tables, Listings and Figures
WBC	White blood cell
WHO	World Health Organization

2 INTRODUCTION / BACKGROUND INFORMATION

This study is a follow on to Protocol LFB-FVIIa-008-14 Amendment 4 (dated 20 December 2016), a phase 3 study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)[1] and will be the basis for the surgery indication of the product, Coagulation Factor VIIa (Recombinant), CCI (CCI This study responds to the deficiencies of the PERSEPT 3 study pointed out by U.S. Food and Drug Administration (FDA) in the Supplemental Biologics License Application (sBLA) review and Type C meeting response.

This Statistical Analysis Plan (SAP) details comprehensive specifications of the efficacy and safety data summaries and statistical analyses in support of the clinical protocol for study F7TG2202 Version 1.0 dated 08 December 2022 and of the corresponding clinical study report (CSR). Tables, listings, and figures (TLF) mock shells and specifications are contained in a separate document. Any deviation from this SAP will be documented in Section 9.8 of the CSR.

2.1 Study objectives

2.1.1 Primary objective

To assess the efficacy of CCI in terms of achieving and maintaining hemostasis in hemophilia A or B patients with inhibitors to FVIII or FIX undergoing elective major surgical procedures.

2.1.2 Secondary objective

To assess the safety of CCI

2.2 Study design

This is an international, multi-center, single-arm, Phase 3, and sequential study. Patients aged 12 to 65 years, inclusive, who have congenital hemophilia A or B with inhibitors and who are scheduled for an elective major surgical procedure will be enrolled. After obtaining informed consent (/child assent for minors) from the patients and/or the patient's parent(s)/legal guardians(s), these patients will undergo screening assessment to determine eligibility. Patients who meet all eligibility criteria and who are deemed adequate by an enrolment committee must be registered within 24 hours prior to surgery in an interactive response system (IRS) by the site staff to be considered as enrolled.

The study schema, visit diagram, and procedures are presented in Figure 1: Study design.

The study duration from first patient in to last patient in is estimated at 16 months, which is to be confirmed by the feasibility study and dependent on the Coronavirus disease 2019 (COVID-19) context. The duration of the patient's participation in the

study (from signing the informed consent/assent form until the follow-up phone call) will be approximately 8 to 12 weeks. A screening period will occur within one month before surgery. The screening and treatment periods may vary from one patient to another.

An external Data Monitoring Committee (DMC) will be set up for this study. The DMC will have two primary responsibilities:

1. The DMC will review the results of the planned interim analysis (to be conducted after 13 patients have been enrolled into the study and their primary efficacy endpoint evaluability determined) to determine if the study should be stopped for efficacy or for futility or continued until the last planned patient to be enrolled has completed the study based on the pre-specified criteria.

2. The DMC will review safety data accrued during the conduct of the study.

The scope of the DMC and interim analysis will be described in a separate SAP.

2.3 Schedule of activities

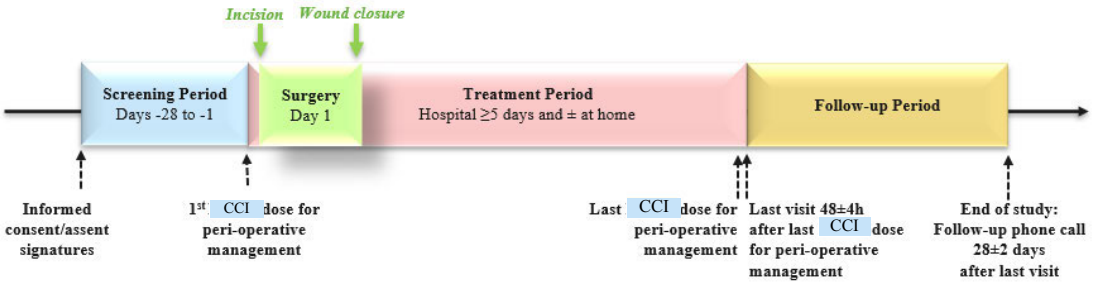
The schedule of activities by visit during the study is shown in Table 1: Schedule of activities.

2.4 Determination of sample size

Given a true proportion of successfully treated major procedure of 0.75, a sample size of 17 evaluable procedures will yield a two-sided 96% confidence interval (CI) with an estimated half-width of 0.197. This assumes a finite population correction based on a population size of 100 under a 1 procedure per patient setting. This translates to a precision estimate of 0.088 for the sample proportion of successfully treated major procedures ($\hat{p}$). Assuming a dropout rate of 10%, a total of 19 procedures are needed to be targeted for the study which translates to an enrolment of 17 patients under a 1 procedure per patient setting.

Figure 1: Study design

1-1: Study Schema



1-2: Visit diagram and procedures

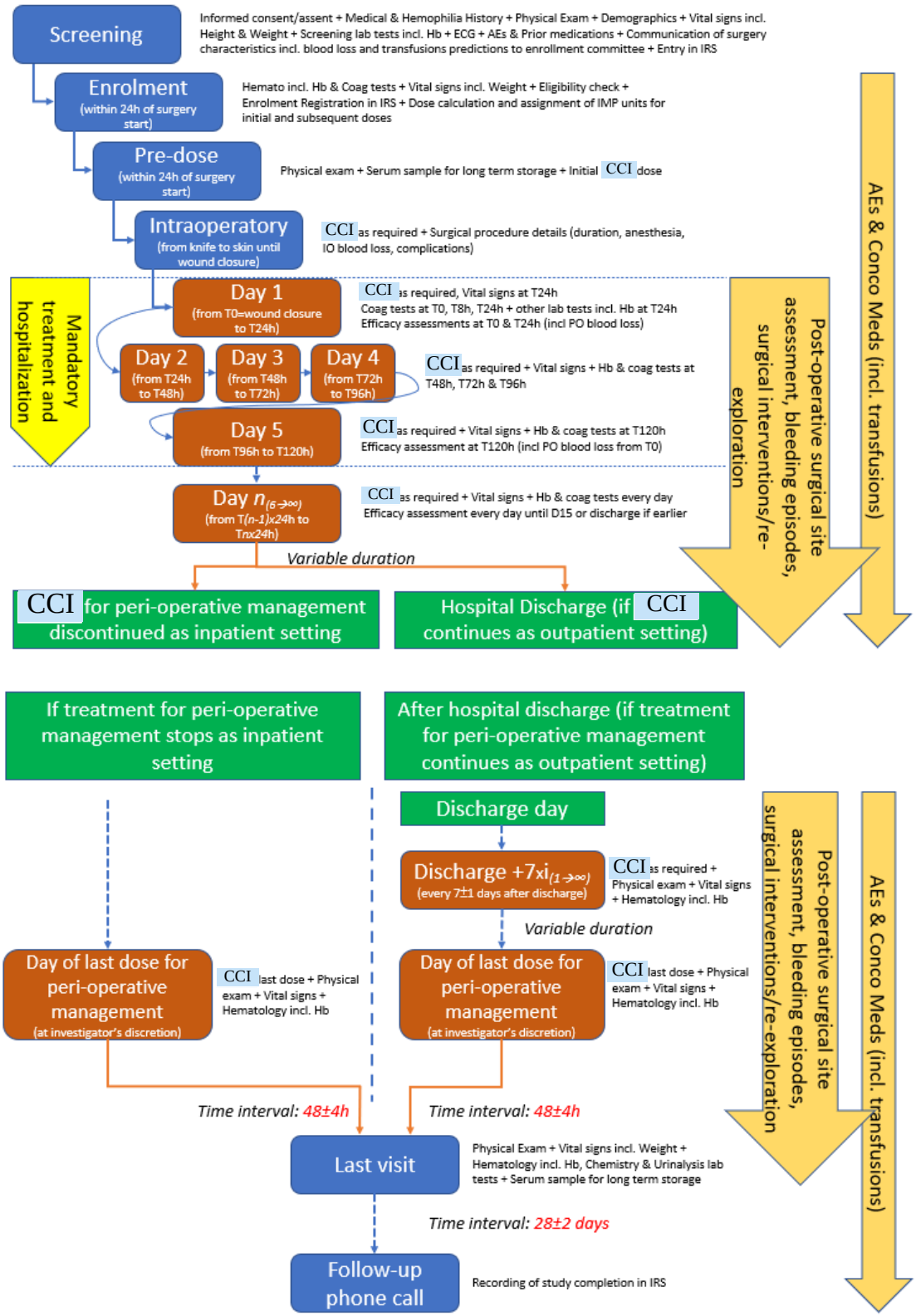


Table 1: Schedule of activities

	Screening period	Treatment period					Follow-up period	
Evaluation/Procedure	**Screening days -28 to -1**	**Prior to surgery**	**During surgery**	**From surgical wound closure to hospital discharge**	**From hospital discharge to last dose of CCI for peri-operative management**	**Last dose of CCI for peri-operative management**	**Last visit 48±4 h after last dose of CCI for peri-operative management or Premature patient discontinuation**	**End of study: Follow-up phone call 28±2 days after last visit**
Informed Consent/Assent	X							
Inclusion/Exclusion Criteria	X	X within 24h						
Demographics and Detailed Medical/Surgical History	X							
Physical Examination	X	X within 24h			X every 7 ± 1 days	X	X	
Post-operative surgical site assessment				X every 24 ± 4 h	X every 7 ± 1 days	X	X	
Laboratory Tests (local)								
Chemistry, Urinalysis	X			X at 24 ± 4 h post-surgical wound closure			X	
Serology	X							
Hematology:								
• Hb	X	X within 24h		X every 24 ± 4 h	X every 7 ± 1 days	X	X	

	Screening period	Treatment period					Follow-up period	
Evaluation/Procedure	**Screening days -28 to -1**	**Prior to surgery**	**During surgery**	**From surgical wound closure to hospital discharge**	**From hospital discharge to last dose of CCI for peri-operative management**	**Last dose of CCI for peri-operative management**	**Last visit 48±4 h after last dose of CCI for peri-operative management or Premature patient discontinuation**	**End of study: Follow-up phone call 28±2 days after last visit**
• Hct, Platelet count, RBC count and WBC count with differential	X	X within 24h		X at 24 ± 4 h post-surgical wound closure	X every 7 ± 1 days	X	X	
• CD4+ cell count	X							
Coagulation:								
• FVIII[12, 14] or FIX[13], PT, aPTT	X							
• ATIII	X[16]							
• Fibrinogen, D-dimer, F 1+2	X	X within 24h		X T0 = wound closure, T8h & every 24 ± 4 h				
Others: FVIII[12,14] or FIX[13] inhibitor titers	X							
IMP (CCI administration[2]		X						
Surgery Characteristics[3]	X		X					
Vital Signs[6]	X[1,8]	X[8]		X every 24 ± 4 h	X every 7 ± 1 days	X	X[8]	
12-Lead ECG	X							
Hemostatic Efficacy Assessments								

	Screening period	**Treatment period**					**Follow-up period**	
Evaluation/Procedure	**Screening days -28 to -1**	**Prior to surgery**	**During surgery**	**From surgical wound closure to hospital discharge**	**From hospital discharge to last dose of CCI for peri-operative management**	**Last dose of CCI for peri-operative management**	**Last visit 48±4 h after last dose of CCI for peri-operative management or Premature patient discontinuation**	**End of study: Follow-up phone call 28±2 days after last visit**
• Surgeon's Intra-operative Assessment[7]				X T0 = wound closure (5)				
• Investigator's Post-operative Assessment[4]				X at 24 ± 4 h and 120 ± 4 h post-surgical wound closure (5), then every 24 ± 4 h until D15 or discharge if earlier				
Surgical interventions/re-explorations for bleeding (if any)				X				
Bleeding episodes (if any)				X				
Adverse Event Assessment	X	X	X[9]					
Phone call[15]					X every 2 ± 1 days			X
Patient's diary				Provided to patient at discharge	Checked at each visit		Checked & collected	
Prior/Concomitant Medication	X							
Serum sample for long term storage[10]		X before 1st CCI dose					X	

	Screening period	Treatment period					Follow-up period	
Evaluation/Procedure	**Screening days -28 to -1**	**Prior to surgery**	**During surgery**	**From surgical wound closure to hospital discharge**	**From hospital discharge to last dose of CCI for peri-operative management**	**Last dose of CCI for peri-operative management**	**Last visit 48±4 h after last dose of CCI for peri-operative management or Premature patient discontinuation**	**End of study: Follow-up phone call 28±2 days after last visit**
Transfusion (if any)[11]		X						

Legends of Table 1

Abbreviations: aPTT, activated partial thromboplastin time; AT III, antithrombin III; D15, Day 15; ECG, electrocardiogram; F 1+2, prothrombin fragment 1+2; FIX, factor IX; FVIII, factor VIII; h, hours; Hb, hemoglobin; Hct, hematocrit; IMP, investigational medicinal product; IV, intravenous; PT, prothrombin time; RBC, red blood cell; WBC, white blood cell

1. *Height will be measured at screening only.*
2. *IMP (CCI Initial dose of 200 µg/kg of CCI will be infused within ≤2 minutes as an IV bolus dose immediately prior to surgical incision. Subsequent doses of 75 µg/kg of CCI will be infused as an IV bolus dose within ≤2 minutes during and after surgical procedure; duration of treatment will be dependent on the patient's status in accordance with Protocol* ***Error! Reference source not found.****.*
3. *Surgical procedure characteristics: Predicted surgery characteristics to complete as per requirements in Protocol Section* ***Error! Reference source not found.****, maximum expected intra- and post-operative blood losses in a similar patient without a bleeding disorder, type of anesthesia. Actual surgery characteristics: duration, estimated intra-operative blood loss, factors that may have influenced bleeding independent of hemostasis, actual type of anesthesia, and complications.*
4. *Including estimated post-operative blood losses from D1 to D15 or discharge if earlier. Post-operative efficacy will be assessed by the investigator or designee and recorded.*
5. *Given the rule in Section 4.2.1, an assessment score will be collected within 12 hours of a missing component score to be used as a replacement. Note that only one missing component score replacement will be allowed.*
6. *Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (oral or tympanic); if the patient is discharged before the 24±4-hour timepoint, vital signs will be taken at that time.*
7. *Intra-operative efficacy will be assessed by the surgeon immediately after surgical wound closure and recorded.*
8. *Weight will be taken at screening, within 24 hours prior to surgery for calculating the dose of CCI throughout the whole treatment period and at last visit.*
9. *Patients will be assessed for signs and symptoms of thromboembolic events, from surgical wound closure until follow-up phone call, such as pulmonary embolism (PE) (e.g. shortness of breath, chest pain, cyanosis) or deep vein thrombosis (e.g. calf pain, swelling/edema, redness, venous distension, pain on dorsiflexion). Patients will also be assessed for signs and symptoms of hypersensitivity reactions from initial to last CCI dose for peri-operative management and at last visit, including but not limited to rash, hives, itching, redness, swelling, edema, allergic rhinitis, watery or itchy eyes, shortness of breath, wheezing, chest tightness, hypotension, etc.*
10. *For purposes of any safety evaluations deemed necessary in the future (e.g. antibodies evaluations)*
11. *Except CD4+ cell count, all hematology tests will be performed in case of the decision for blood component transfusion. The trigger for blood component transfusion based on whether Hb level is Hb <7 g/dL. When Hb is ≥7 g/dL and <8 g/dL, blood component transfusion is allowed at investigator's discretion dependent on patient status. Expected number and volume of blood component transfusion in a similar patient without a bleeding disorder in the same procedure will be predicted by the surgeon prior surgery and recorded.*
12. *In hemophilia A patients only*

13. *In hemophilia B patients only*
14. *Bovine chromogenic for emicizumab patients*
15. *Phone call from the investigator or designee to the patient will be planned to ask/record adverse events, discuss dosing regimen, ask about physical therapy visits, remind for diary completion.*
16. *AT III must be performed at screening and reported in the eCRF only for patients with a history of treatment with fitusiran*.

3 ANALYSIS SETS

3.1 Enrolled population

Enrolled population consists of eligible patients (meeting all inclusion/exclusion criteria) for whom an informed consent is signed and, where applicable according to local regulation, for whom an assent is also signed in case the patient is minor. Please note this definition of enrolled population is different from the enrolled population defined in the protocol, in which screen failed patients are included.

3.2 Full analysis set (FAS)

Full Analysis Set (FAS) is defined as all major procedures conducted from patients enrolled into the study who had received at least one dose of CCI

3.3 Per protocol (PP)

The Per Protocol (PP) population is a subset of the FAS for which the procedures correspond to patients who complied sufficiently with the protocol in terms of exposure to treatment, availability of measurements, and absence of major or important protocol deviations (PD) to impact the primary efficacy endpoint.

Classification of patients or procedures into (or exclusions from) the PP will be determined in the PD review meeting(s) prior to interim analysis and database lock (final analysis) to avoid bias, with the support of the Protocol Deviations Guidance (PDG).

Patients or procedures excluded from PP population and the reasons for exclusion will be summarized by patient type (exposed to emicizumab and naïve to emicizumab). A listing will be provided as well.

If the difference between FAS and PP population in terms of number of patients is no greater than 30%, then PP analysis will not be performed.

3.4 Safety population (SAF)

The safety population (SAF) will include all patients who took at least one dose of CCI

4 STUDY ENDPOINTS

4.1 Primary endpoint

The primary efficacy endpoint is the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response (Appendix 1: Global hemostatic response based on the individual scores during the intra-operative period and at 24 and 120 hours after surgical wound closure).

The global hemostatic response score is obtained by summing assigned scores from a defined 4-point hemostatic scale (excellent: score = 3, good: score = 2, moderate: score = 1, poor: score = 0; see protocol section 9.2) determined:

- at wound closure (T0) (based on data collected during the intra-operative (IO) period) **and**,
- at 24 hours after surgical wound closure (based on data collected during the 24-hour post-operative (PO) period, i.e., 0-24 hours period) **and**,
- at 120 hours after surgical wound closure (based on data collected during the 120-hour PO period, i.e., 0-120 hours)

The global hemostatic response will be considered:

- Excellent if the aggregate score from the 3 timepoints is between 7 and 9, inclusive, with no score <2 for any of the component score comprising the aggregate score
- Good if the aggregate score from the 3 timepoints is between 5 and 7, inclusive, with no IO and 120-hours PO scores <2 and no 24-hours PO score <1
- Moderate if the aggregate score from the 3 timepoints is between 3 and 7, inclusive, with no score <1 for any of the component score comprising the aggregate score or between 5 and 6, inclusive, when including a score = 0 or missing (without a replacement score) for any of the component score comprising the aggregate score
- Poor if the aggregate score from the 3 timepoints is between 0 and 4, inclusive, when including at least 1 score = 0 or missing (without a replacement score) for any of the component score comprising the aggregate score.

4.2 Secondary endpoints

4.2.1 Secondary efficacy endpoints

Secondary efficacy endpoints include the following:

- Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale at **each** of the following assessment timepoints:
  1. During the IO period,
  2. At 24 hours after surgical wound closure (based on data collected during the 24-hour PO period, i.e., 0-24 hours period),
  3. At 120 hours after surgical wound closure (based on data collected during the 120-hour PO period, i.e., 0-120 hours period).
- Proportion of successfully treated major procedures defined by a good or excellent global hemostatic response based on the 4-point hemostatic scale as assessed by the investigator at **each** timepoint post 120 hours after surgical wound closure.

- Mean difference between actual measurable IO blood loss and maximum predicted blood loss in a similar patient without a bleeding disorder for the same major procedure.
- Mean difference between actual measurable PO blood loss (measured by the amount of drainage in mL where, and for the duration, drain is needed) and maximum predicted blood loss in a similar patient without a bleeding disorder for the same major procedure at each of the following assessment timepoints:
  1. At 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e., 0-24 hours period),
  2. At 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e., 0-120 hours period).
- Mean difference between actual blood product transfusion and maximum predicted blood product transfusion in mL in a similar patient without a bleeding disorder for the same major procedure at each of the following assessment timepoints:
  1. At wound closure (based on data collected during the IO period),
  2. At 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e., 0-24 hours period),
  3. At 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e., 0-120 hours period).
- Mean amount of CCI used to maintain hemostasis during surgery and post-surgery, where amount is calculated in terms of aggregate amount (total) during surgery (including dose administered prior to surgical incision) through post-surgery, and separated by use: during surgery (including dose administered prior to surgical incision) through Day 5 (D5), all hospital stays, at home, or for specific reasons (e.g., physical therapy, or other reasons like tourniquet, drain or suture removal)
- Mean number of bleeding episodes at the surgical site between surgical wound closure and last visit
- Mean number of surgical intervention/re-explorations for bleeding episodes between surgical wound closure and last visit
- Number of deaths from bleeding attributed to ineffective hemostasis.

4.2.2 Other secondary endpoints

Other secondary endpoints include:

- Mean change in hemoglobin (Hb) level from initiation of the surgery until last visit.
- Number and incidence of treatment emergent adverse events (TEAEs) (i.e., all AEs that occur at the time of or after the investigational medicinal product (IMP) administration until follow-up phone call) and adverse events of special interest (AESIs) (i.e., thromboembolic events and hypersensitivity reactions)
- Mean value at each timepoint and mean change from baseline to each post-baseline timepoint in clinical laboratory parameters (continuous); proportion for each response category at each timepoint and proportion for each response category shift from baseline to each post-baseline timepoint in clinical laboratory parameters (discrete)
- Mean value at each timepoint and mean change from baseline to each post-baseline timepoint in vital signs.

- Proportion for each response category at each timepoint and proportion for each response category shift from baseline to each post-baseline timepoint in physical examination
- Mean value at each visit and mean change from baseline to each visit in coagulation-related parameters [including fibrinogen, D-dimer, and Prothrombin fragment F 1+2 (F 1+2) levels]

4.3 Exploratory endpoint

The exploratory endpoint is the mean number of days in intensive care unit (ICU) and hospital starting from the day of surgery until hospital discharge.

5 STATISTICAL/ANALYTICAL ISSUES

5.1 Adjustment for covariates

No covariate will be considered.

5.2 Handling of dropouts missing data and outliers

5.2.1 Dropouts

Patients will be followed until the scheduled end of the study, independently of their adherence to the treatment schedule. Patients who withdraw their consent will be asked to undergo the assessment scheduled at the last visit (48±4 hours after last dose of CCI for peri-operative management or premature patient discontinuation), to collect key efficacy/safety data unless the patient objected to the collection of further data when withdrawing consent. Reasons for not completing key efficacy and/or safety assessment will be collected.

5.2.2 Missing data

5.2.2.1 Global Hemostatic Response Score Data

All means will be put in place to minimize missing data, especially for the primary efficacy endpoint (Section 4.1). If for some reason one of the component scores comprising the aggregate score is missing (i.e., one of the scores to be assigned during the IO period, at 24 hours, or at 120 hours after surgical wound closure is missing), an assigned score collected within a window of 12 hours from the assessment timepoint (corresponding to the missing component score) will be used to replace the missing component score. Note that only one missing component score replacement will be allowed.

5.2.2.2 Other Data

If a scheduled visit assessment value is missing [for laboratory values, vital signs, and electrocardiograms (ECG)] and no re-test or repeat value is available, the non-missing value at the unscheduled visit closest to the scheduled visit will be used in the summary tables.

5.2.3 Missing or incomplete dates

Missing or incomplete dates will be imputed to determine certain flags for treatment emergent adverse event (TEAE) and prior/concomitant medication. The imputation rules of missing or incomplete dates are described in Appendix 2: Imputation for Missing or Incomplete Dates.

5.2.4 Outliers

Outliers, if any, will be identified **prior to database lock.** In case an outlier which is impossible/implausible is identified, the primary analysis on the primary efficacy endpoint will still be based on all data. A supportive analysis with outliers excluded will be performed.

5.3 Randomization

Not applicable as this is a single-arm study.

5.4 Interim analyses and data monitoring

5.4.1 Maintaining the blind

No blinding is involved since this is a single-arm study.

5.4.2 Interim analyses

An interim analysis will be performed by an external DMC when approximately 75% of the evaluable patients have been enrolled (13 of 17) and their primary efficacy endpoint evaluability determined.

The interim analysis will be performed on the primary efficacy endpoint using the FAS and PP population and supportive secondary efficacy endpoints using the FAS (and PP population for the first two endpoints. See Table 2: Allocation of type I error for each). A 99% two-sided confidence interval (CI) for the primary efficacy endpoint will be calculated based on the Clopper-Pearson exact method[2].

Stopping for efficacy
Stopping for efficacy requires rejection of the null hypothesis, i.e., showing a two-sided lower confidence bound that is greater than or equal to 0.55, i.e., the procedures result in at most 1 failure.
If stopping for efficacy is claimed, the study will proceed as follows:

- No additional patients will be enrolled;
- All patients that have been enrolled will continue to the last visit, after which the database will be locked; and
- All analyses described in this SAP will be performed after the database lock.

Stopping for futility
If the number of observed failures is at least 4, then the study will be terminated for futility.
If stopping for futility is claimed, the study will proceed as follows:

- No additional patients will be enrolled and the study will be early terminated;
- Patients in the study who have not completed their visit will continue to their early termination visit, after which the database will be locked; and

- All safety analyses described in this SAP will be performed after the database lock. Abbreviated efficacy analysis of primary and secondary efficacy endpoints will be performed as well.

Continuing the study to 17 evaluable patients
If the criteria of stopping for efficacy and stopping for futility are not met, the study will proceed as follows:

- The study will continue to enroll patients to reach 17 evaluable patients in total;
- All patients will continue to the last visit, and then the database will be locked; and
- All analyses described in this SAP will be performed at the final analysis after the database lock.

5.5 Pooling of centers

The statistical models to be used in analyzing the study's endpoints will not be adjusted for differences between centers. Data from all centers will be pooled to be included in the analyses.

5.6 Subgroups analyses and multiplicity issues

5.6.1 Examination subgroups

Analyses will be performed based on patient type (exposed to emicizumab or naïve to emicizumab) for the primary efficacy and secondary endpoints.

5.6.2 Multiplicity

With the sequential design in this study, the Type I error of 0.05 will be allocated as 0.01 and 0.04 between interim and final analysis (Table 2: Allocation of type I error for each). For primary efficacy endpoint, in order to control for multiplicity, a 99% two-sided confidence interval (CI) based on Clopper-Pearson method will be calculated at the time of interim analysis. Should the study progress to complete the enrolment of 17 evaluable patients, a 96% two-sided CI based on the Clopper-Pearson exact method will be calculated at final analysis.

Table 2: Allocation of type I error for each analysis

	Type I Error	Confidence Level	Number of Evaluable Patients
Interim analysis	0.01	99%	13
Final analysis	0.04	96%	17

In general, analyses of the secondary endpoints will involve the calculation of a point estimate together with the associated 95% CI. The calculated CIs will not be adjusted for multiplicity.

5.7 Other issues

5.7.1 Significance testing and estimation

The main null hypothesis to be tested for the primary efficacy endpoint, i.e., proportion of successfully treated major procedures as defined in Section 4.1 is that the proportion is less than 0.55 against the alternative hypothesis that the proportion is at least 0.55. The outcome in terms of the sample proportion of successfully treated major procedure will be interpreted as positive if the lower bound of the associated confidence interval (CI) based on the Clopper-Pearson method is at least 0.55. In this case, the null hypothesis is rejected in favour of one-sided alternative hypotheses showing a high incidence of treatment success (or lower incidence of treatment failure). Given that the study is designed as a sequential study, the null and alternative hypotheses will be evaluated as necessary at each evaluation timepoint, i.e., interim analysis and final analysis (see Sections 5.4.2 and 5.6.2).

5.7.2 Experimental units

In this study, the experimental unit is the major procedure conducted from patients enrolled into the study for efficacy analyses and patient for safety analyses.

6 ANALYSIS METHODS

6.1 General considerations

This section describes the data analysis and presentation conventions that will be applied in this study.

6.1.1 Data presentation

Data will be presented following general practice, mathematical rationale, or scientific rationale (e.g., age should be presented in whole numbers). For decimal places in numeric variables, raw data will be presented to the number of decimal places collected, and derived data will be presented to an appropriate number of decimal places following mathematical or scientific rationale.

For summary statistics of continuous data, the following will be presented, number of non-missing values (n), number of missing values, arithmetic mean, standard deviation, median, and the range (minimum, maximum), unless otherwise specified.

Categorical data will be summarized with the number of patients at the relevant time point (n), number of missing observations, frequency counts, and percentage. Percentage will be calculated using the number of non-missing values as the denominator, unless otherwise specified. When a percentage is summarized, the denominator will be specified in the footnote of the display.

Confidence intervals (CIs) will be calculated unadjusted and two-sided with the confidence level specified for each analysis (e.g., for primary efficacy endpoint, 99% CI for interim analysis and 96% CI for final analysis; 95% CI for other endpoints).
The number of decimal places presented in the summary statistics follows the conventions listed in Table 3: Number of decimal places for summary statistics.

Table 3: Number of decimal places for summary statistics

Statistics	**Rule**
Minimum / Maximum	Same precision as the raw data.
Mean	1 decimal place greater than the raw/derived data
Median / Quartile / Percentiles	
Confidence interval bounds	
Standard deviation	2 decimal places greater than the raw/derived data
Standard errors of the mean (SE)	
Percentages 0% 100%	1 decimal place ‘-‘ No decimal place
P-values P-values which are less than 0.0001	4 decimal places (p=0.xxxx) ‘<0.0001’

6.1.2 Report outputs presentation

All text fields must be left justified. Numeric or numeric with some text specification (e.g., <4.5) must be decimal justified. Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

Summary table will be presented by patient type and overall, unless otherwise specified.

Listings will be sorted by patient type, patient identification number (ID), and by visit week/day within each patient, when appropriate.

All report outputs will be produced using Statistical Analysis System (SAS)® v9.4 or latest version in a secure and validated environment. All report outputs will be provided in both rich text format (rtf) and portable document format (pdf) documents.

6.2 Analyses of efficacy

Efficacy endpoints will be analyzed using the FAS. Supportive analysis of the efficacy endpoints, including the primary efficacy endpoint and the secondary efficacy endpoints indicated in Table 6: Analysis of secondary efficacy endpoints, will also be performed on PP population. However, if the difference between FAS and PP population in terms of number of patients is not greater than 30%, PP population analysis will not be performed. For example, if number of patients included in PP population is greater than 10 in the interim analysis, or greater than 12 in the final analysis, PP population analysis will be omitted.

6.2.1 Primary efficacy endpoint

The primary efficacy endpoint is defined as the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response based on assigned scores from a defined 4-point hemostatic scale during the IO period, at 24 and 120 hours after surgical wound closure.

6.2.1.1 Definition of estimand

For the objective of evaluating the efficacy of CCI in terms of achieving and maintaining hemostasis, the estimand is defined as follows:

- **Target population:** elective major surgical procedures of hemophilia A or B patients with inhibitors to FVIII or FIX enrolled in the study.
- **Treatment condition:** the initial CCI dose of 200 µg/kg followed by repeated administration of doses of 75 µg/kg of CCI to manage bleeding associated to surgery.
- **Endpoint:** proportion of successfully treated major procedures defined by a good or excellent global hemostatic response.

- **Population-level summary:** the proportion and associated Clopper-Pearson exact CI of the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response.

Intercurrent events and strategies: Intercurrent events identified include withdrawal from assigned treatment and initiation of alternative/rescue therapy. The handling strategies of these intercurrent events are described in Table 4: Intercurrent Event Strategies for the Primary Analysis below.

Table 4: Intercurrent event strategies for the primary analysis

Intercurrent Event	Handling Strategy
Withdrawal from assigned treatment	Treatment policy strategy: Intercurrent event is ignored; Estimated effect will be based on study drug planned/received per protocol and on FAS.
Initiation of alternative/rescue therapy	Composite variable strategy: Missing treatment effect (response is censored) set as failure if intercurrent event is indicative of lack of efficacy.

6.2.1.2 Primary analysis of the primary endpoint

A proportion and the associated Clopper-Pearson exact CI of the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response will be calculated at each evaluation milestone (i.e., interim analysis and final analysis). This will be summarized by total number of procedures as well as by patient type.

6.2.1.3 Sensitivity analyses of the primary endpoint

Sensitivity analyses will be conducted to assess the impact of missing data and the robustness of the primary analysis. Data handling approaches for intercurrent events in the sensitivity analyses are described in Table 5: Intercurrent Event Strategies for Sensitivity Analyses.

Table 5: Intercurrent event strategies for sensitivity analyses

Intercurrent Event	Handling Strategy
Withdrawal from assigned treatment	Same as primary analysis (treatment policy strategy)
Initiation of alternative/rescue therapy	1. Hypothetical strategy: Assessments obtained on or after the use of alternative/rescue therapy will be treated as missing. Multiple imputation will be utilized to impute missing assessments with the assumption of missing at random (MAR) (Appendix 4). 2. Treatment policy strategy: Intercurrent event is ignored; Estimated effect will be based on study drug planned/received per protocol and on FAS.

Similar to the primary analysis, a point estimate and the associated Clopper-Pearson exact CI of the proportion of successfully treated major procedures defined by a good

or excellent global hemostatic response will be calculated at each evaluation milestone (i.e., interim analysis and final analysis). This will be summarized by total number of procedures as well as by patient type.

6.2.1.4 Other analyses of the primary endpoint

Supportive analysis of the primary efficacy endpoint will also be performed on PP population if the difference between FAS and PP population in terms of number of patients is greater than 30%.

A forest plot will be generated to illustrate the point estimate and the associated Clopper-Pearson exact CI for each patient type and overall.

6.2.2 Secondary efficacy endpoints

The secondary efficacy endpoints are listed, and detailed analysis are included in Table 6: Analysis of secondary efficacy endpoints.

Table 6: Analysis of secondary efficacy endpoints

Secondary Endpoints	Population	Analysis
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale determined at wound closure (T0) (based on data collected during the IO period) , at 24 hours after surgical wound closure (based on data collected during the 24-hour PO period, i.e. 0-24 hours period) and at 120 hours after surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours)	FAS and PP*	Analysis will involve calculation of a point estimate and the associated Clopper-Pearson exact CI at each evaluation timepoint. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab). A forest plot will be generated to illustrate the point estimate along with Clopper-Pearson exact CI of the global hemostatic response and at each evaluation timepoint by patient type and overall.
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale by the **investigator** at each timepoint post 120 hours after surgical wound closure	FAS and PP*	Analysis will involve calculation of a point estimate and the associated Clopper-Pearson exact CI at each evaluation timepoint. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab).
Mean difference between actual measurable blood loss and maximum predicted blood loss in a similar patient without a bleeding disorder for major procedures during the IO period	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the t-distribution. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab, if data permits).
Mean difference between actual measurable PO blood loss (measured by the amount of drainage in mL where, and for the duration, drain is needed) and maximum predicted blood loss in a	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the t-distribution at each evaluation timepoint. This will be done based on total number

Secondary Endpoints	Population	Analysis
similar patient without a bleeding disorder for the same major procedure at each of the following assessment timepoints: at 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e. 0-24 hours) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours)		of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab, if data permits).
Mean difference between actual blood product transfusion and maximum predicted blood product transfusion in mL in a similar patient without a bleeding disorder for the same major procedure at each of the following assessment timepoints: at wound closure (based on data collected during the IO period), 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e. 0-24 hours) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours)	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the t-distribution at each evaluation timepoint. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab, if data permits).
Mean amount of CCI used to maintain hemostasis during surgery and post-surgery, where amount is calculated in terms of aggregate amount (total) during surgery (including dose administered prior to surgical incision) through post-surgery and separated by use: during surgery (including dose administered prior to surgical incision) through D5, all hospital stay, at home, or for specific reasons (e.g. physical therapy, or other reasons like tourniquet, drain or suture removal)	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the t-distribution at each evaluation timepoint. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab, if data permits).
Mean number of bleeding episodes at the surgical site between surgical wound closure and last visit	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the Poisson distribution (Negative Binomial if over dispersed). This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab).
Mean number of surgical interventions/re-explorations for bleeding episodes between surgical wound closure and last visit	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the Poisson distribution (Negative Binomial if over dispersed). This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab).
Number of deaths from bleeding attributed to ineffective hemostasis	FAS	Analysis will involve calculation of a point estimate and the associated CI

Secondary Endpoints	Population	Analysis
		based on the Poisson distribution (Negative Binomial if over dispersed). This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab).

*Analysis using PP population will be performed if the difference between FAS and PP population in terms of number of patients is greater than 30%.

Post-operative response assessments, transfusions, surgical intervention or invasive procedures, and bleeding episodes will also be listed in data listings.

Spaghetti plots will be generated for each patient included in FAS for the endpoints listed below:

- Blood product transfusion and hemostatic response assessment over time
- Actual blood loss and hemostatic response assessment over time
- CCI administered and hemostatic response assessment over time.

6.2.3 Exploratory analysis

The exploratory efficacy endpoint is listed, and detailed analyses are included in Table 7: Analysis of exploratory efficacy endpoint.

Table 7: Analysis of exploratory efficacy endpoint

Exploratory Endpoint	Population	Analysis
Mean number of days in ICU and hospital starting from the day of surgery until hospital discharge	FAS	Analysis will involve calculation of a point estimate and the associated CI based on the t-distribution. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab, if data permits).

6.3 Safety analyses

All safety data included in the summary tables and data listings will be based on the SAF population, unless otherwise specified.

No hypothesis testing will be performed in safety analyses.

6.3.1 Extent of exposure

The exposure analysis is a part of the secondary efficacy endpoint analyses in this study (Section 6.2.2). Besides the analyses listed in Section 6.2.2, displays described in this section will be generated as well.

Exposure as measured by total amount of CCI (µg/kg) and total amount of CCI (mg) administered, number of administrations, and total duration of exposure (days) will be summarized. The summary statistics include the first and third quartiles besides the statistics listed in Section 6.1.1: Data presentation.

Duration of treatment (days) will be calculated as (last dose date – first dose date) + 1.

Amount of study drug (mg) will be calculated as total amount of study drug administered as reported in CRF page. Negative amount of study drug will be excluded from summary calculations.

Treatment exposure and treatment compliance measures will be listed.

6.3.2 Adverse events

Adverse events will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) with reference to System Organ Class (SOC) and Preferred Terms (PT). All displays will be summarized by SOC and PT, unless otherwise specified.

Below are the general rules for AEs summary:

1. Patients will be classified as having withdrawn from the study due to an AE if the patient has a study drug action taken recorded as 'Drug withdrawn' on the AE electronic Case Report Form (eCRF) page and patient has a recorded 'No' for the study completion item with 'AE' as the primary reason of discontinuation on the corresponding eCRF page.
2. When counting the number of patients with AEs, if a patient experiences the same AE (same PT) more than once, the patient is only counted once for the PT of interest.
3. AEs related to CCI tables include only those AEs with a relationship to study drug of 'related' or if there is a missing relationship on the AE eCRF page.
4. For AE severity, the following rules will be applied in determining the number of patients with AEs:
   - A patient who experiences two AEs of the SAME PT of the SAME severity will be counted ONCE under the severity for the PT of interest.
   - An AE with missing severity will be kept with missing severity.

An overall summary table of different subsets of AEs will be presented. AE results will also be summarized by relationship to CCI and severity (mild, moderate, severe). All reported AEs will be presented in a listing, sorted by patient type, patient ID, start time of AEs, primary SOC, and PT for all AEs recorded during the study.

Listings of serious adverse events (SAEs), adverse events leading to study discontinuation, and deaths will also be presented.

6.3.2.1 Treatment emergent adverse events

An AE will be considered as treatment-emergent adverse event (TEAE) if it occurs at the time of or after CCI administration until follow-up phone call, or starts prior to CCI administration and increases in severity after CCI administration.

Handling missing or incomplete dates is described in Appendix 2: Imputation for Missing or Incomplete Dates.

An overall summary will be provided, including the number and percentage of patients with AEs and incidence of AEs. The summary will also be provided by SOC, PT, and by the following categories defined below:

- Non-serious TEAEs
- Treatment-emergent serious adverse events (TESAEs)
- Common TEAE (defined as TEAEs reported by 2 or more patients in any patient type)
- TEAEs leading to study discontinuation
- TEAEs by severity
- Study drug related TEAEs
- TEAEs by outcome

6.3.2.2 Treatment-emergent adverse events of special interest

In this study, adverse events of special interest (AESIs) include thromboembolic events and hypersensitivity reactions.

Treatment-emergent AESI (TEAESI) is defined as AESI that occurs at the time or after CCI administration until follow-up phone call.

A summary table of TEAESIs will be presented, including the number and percentage of patients with at least one TEAESI and incidence of TEAESIs. The summary of TEAESIs will also be provided by AESI category, SOC, PT, and by the following categories defined below:

- Non-serious TEAESIs
- Treatment-emergent serious adverse events of interest (TESAESIs)
- TEAESIs leading to study discontinuation
- TEAESIs by severity
- Study drug related TEAESIs
- TEAESIs by outcome

6.3.3 Clinical laboratory evaluation

All planned laboratory tests (including hematology, serum chemistry, coagulation, urinalysis [dipstick + microscopic examination of sediments in case of positive dipstick], serology, and other) for this study are listed in Appendix 3.

All laboratory values will be reported in standard international (SI) unit. Summary displays for laboratory data will be presented. For tables presenting minimum and/or maximum result and abnormalities (not by scheduled visit), unscheduled visit results will be included.

All collected laboratory assessments will be listed with unscheduled assessments included. Assessments outside the normal ranges will be flagged (High [H], Low [L], clinically significant [C]) where applicable.

6.3.3.1 Hematology and serum chemistry

For hematology and serum chemistry laboratory assessments, descriptive statistics of actual values and change from baseline for each parameter will be presented.

Data will be further categorized into different categories with reference to laboratory normal ranges, including low (below lower limit of normal), normal, and high (above upper limit of normal). Shift tables summarizing the changes in normal range categories from baseline to end of study (EoS) will be provided for all scheduled post-baseline visits.

Abnormal laboratory results will be summarized with number and percentage of patients and presented by patient type and overall, at each scheduled visit.

Spaghetti plots will be generated for hemoglobin and hemostatic response assessment over time for patients included in FAS.

6.3.3.2 Urinalysis (dipstick + microscopic examination of sediments in case of positive dipstick)

Urinalysis tests will be performed at screening, 24±4 hours after surgical wound closure, and the last visit.

Urinalysis results will be summarized with the original reported categories and also with the percentage of normal, abnormal (including not clinically significant and clinically significant), not reliable, and "not done" by scheduled visit. Shift table summarizing the changes in the categories of normal, abnormal (including not clinically significant and clinically significant) from baseline to EoS will be provided for all scheduled post-baseline visits.

6.3.4 Vital signs

Vital signs included in this study are systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and body temperature. Data will be collected at screening, prior to surgery, every 24±4 hours after surgical wound closure until hospital discharge, every 7±1 days after hospital discharge until last dose of CCI for peri-operative management, at last dose of CCI for peri-operative management, and last visit (48±4 hours after last dose of CCI for peri-operative management or premature patient discontinuation).

Vital signs will be summarized descriptively, including the reported value at each scheduled visit and the change from baseline to each scheduled post-baseline visit.

Vital signs data will be further categorized into different categories with reference to normal ranges (Table 8: Vital signs abnormality criteria), including low (below lower limit of normal), normal, and high (above upper limit of normal) for respiratory rate, temperature, and heart rate, or normal, high (above normal range) for SBP, DBP. Shift tables summarizing the changes in normal range categories from baseline to EoS will be provided for all scheduled post-baseline visits.

Table 8: Vital signs abnormality criteria

Vital Sign Parameter (units)	Normal (Reference) Range
SBP (mmHg)[1]	<120
DBP (mmHg)[1]	<80
Respiratory rate (bpm)	12-18
Temperature (°C)	35.5 – 39.5
Heart Rate[1]	Resting: 60 - 100

[1] American Heart Association classifications

Abnormal vital sign results will be summarized with the number and percentage of patients with reported abnormality.

A listing of vital signs, including assessments at unscheduled visit, will be provided. In the listing, reported assessment out of the normal range (Table 8: Vital signs abnormality criteria) will be flagged.

6.3.4.1 Weight and height

Body weight will be summarized descriptively. Height will be collected at screening visit only and will be summarized.

6.3.5 Physical examinations

Physical examination findings (normal, abnormal [including not clinically significant, clinically significant]) will be summarized with percentage at each scheduled timepoint by body system, and by patient type and overall. Shift tables summarizing the changes in normal range categories from baseline to EoS will be provided for all scheduled post-baseline visits.

A listing of physical examinations will be also provided.

6.3.6 Other observations related to safety

6.3.6.1 Electrocardiograms

Electrocardiograms (ECGs) assessment will be collected at screening visit. The interpretation of assessment (normal, abnormal [not clinically significant and clinically

significant]) will be summarized with the number and percentage of patients with the specific result.

ECG assessment will be listed.

6.3.6.2 Serology

Serology test will be collected at screening visit, including hepatitis B surface antigen, anti-HIV 1 & 2 antibodies for HIV, and anti-HCV antibodies by polymerase chain reaction (PCR) for HCV. Data will be summarized descriptively with number and percentage of patients with the test results (positive/negative/not done).

Serology test data will also be listed.

6.3.6.3 Coagulation and other test

Coagulation tests planned to be collected only at screening visit are FVIII/FIX activity, prothrombin time, activated partial thromboplastin time (aPTT), and, under conditions, antithrombin III (AT III). Other test including FVIII or FIX inhibitor titer is planned at screening visit only. The actual reported values of these parameters will be summarized descriptively.

Coagulation-related parameters, including fibrinogen, D-dimer, and F 1+2 will be collected at screening, within 24 hours prior to surgery, time at wound closure, 8 hours after wound closure, and every 24±4 hours from surgical wound closure to hospital discharge. For these parameters, the actual value and the change from baseline to each post-baseline visit will be summarized by scheduled visit. Data collected during each visit and for each patient will be further categorized “low”, “normal”, “high”, “not reliable”, or “not done” with reference to individual parameter normal range (Refer to Local Lab Conventions). Shift tables summarizing the changes in normal range categories from baseline to the last visit from surgical wound closure to hospital discharge will be provided for all scheduled post-baseline visits, with number and percentage of patients included in each category. Abnormal coagulation test results will be summarized with the number and percentage of patients.

Coagulation tests data will also be listed, with records categorized as abnormal and clinically significant flagged.

6.4 Study patients

6.4.1 Patient disposition

Patient disposition will be presented using the following summary tables:

- A summary table will be provided with the number of patients screened, screen failed, and enrolled. For screen failures, the reason for screen failure will be summarized with count and percentage. The percentage will be based on the number of patients screened as 100%.

- A summary table will be provided with the number of patients enrolled, completed the study, withdrew from the study, number of deaths, patients included in FAS, PP population, and SAF. For patients withdrawn from the study, the primary reason for withdrawal will be summarized with counts and percentages. This table will be presented by patient type and overall. The percentage will be based on the number of enrolled patients as 100%.

All screened patients will be listed and the reasons for screen failures will be included.

All enrolled patients will be listed. The study completion status (i.e., completed or withdrawal) will be included together with the reasons for study withdrawal.

6.4.2 Protocol deviations

The protocol deviations are managed according to the PDG. Protocol deviations will be assessed as "non-important" or "important" during PD review meetings.

An important subset of protocol deviations is "important protocol deviations", which are defined by International Conference on Harmonisation (ICH) E3 as protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. Deviations not classified as important will be assigned as non-important.

According to the definition of "important protocol deviations" in ICH E3 guidelines, the following items will be assessed as important protocol deviations, unless decided otherwise during the PD review meetings:

- Important deviation of inclusion/exclusion criteria
- Use of prohibited medication
- Missed protocol directed dose of CCI
- Patient met withdrawal criteria but not withdrawn
- Patient failed to report SAE
- Inadequate informed consent administration
- Early discontinuation due to any reason other than lost to follow-up or consent/assent withdrawal for which the patient does not have an end-of-study visit.

Important protocol deviations will be summarized by patient type and overall.

All protocol deviations as well as important protocol deviations will be listed.

6.5 Demographics and other baseline characteristics

Baseline measurement is defined as the latest non-missing assessment prior to the first dose of CCI

6.5.1 Demographics

Demographic and baseline characteristics data will include age (years), sex, race, ethnicity, weight and height at baseline, body mass index (BMI) calculated using

weight and height from screening visit. The summary table will be provided and be based on the SAF population.

All demographic and baseline characteristics will be listed.

6.5.2 Disease characteristics

The following disease characteristic will be summarized based on the SAF population.

- Type of hemophilia (Type A, Type B)
- Hemophilia severity at screening (Mild, Moderate, Severe)
- Hemophilia factor (Factor VIII, Factor IX)
- Factor VIII level or Factor IX level (%)
- FVIII/FIX Inhibitor status (Bethesda units [BU] ≥5, BU <5)
- History of immune tolerance induction (ITI) Therapy (Yes, No)
- History of other prophylactic treatment within last 6 months
- History of other curative treatment within last 6 months

6.5.3 Medical and surgical history

Medical and surgical history will be coded using the latest version of MedDRA with SOC and PT.

A frequency table of the number and percentage of patients will be provided for all medical and surgical history by primary SOC and PT term for each patient type and overall.

A listing will be provided. The listing will be sorted by patient type, patient ID, primary SOC, PT.

6.5.4 Surgery characteristics

Surgery characteristics will be summarized. The following characteristics will be included in the summary:

Surgery characteristics

- Procedure
- Predicted type of anesthesia
- Dosing regimen of emicizumab use
- Planned use of antifibrinolytics (Yes, No)
- Expected maximum blood loss (mL) for the same procedure for a similar patient without a bleeding disorder during the:
  - IO period (from surgical incision until wound closure)
  - 24 hours PO period (from surgical wound closure until 24 hours post wound closure)
  - 120 hours PO period (from surgical wound closure until 120 post wound closure – cumulative prediction across the PO time, including the volume expected for the 24 hours PO period)

  - Subsequent days until Day 15 (D15) or hospital discharge if earlier
- Expected maximum number of units and volume (in mL) of blood component transfusions for the same procedure for a similar patient without a bleeding disorder during the:
  - IO period (from surgical incision until wound closure)
  - 24 hours PO period (from surgical wound closure until 24 hours post wound closure)
  - 120 hours PO period (from surgical wound closure until 120 post wound closure – cumulative prediction across the PO time, including the volume expected for the 24 hours PO period)
  - Subsequent days until D15 or hospital discharge if earlier
- Actual type of anesthesia
- Surgery duration (hours)
- Estimated IO blood loss
- Surgery complications (Yes/No) (e.g., haemorrhagic, infections, hemodynamic, cardiopulmonary, thromboembolic, impaired wound healing, genitourinary, and others)

Surgery characteristics will be listed by patient type and patient ID.

6.5.5 Prior and concomitant medication, therapies/procedures

Prior and Concomitant medications/therapies will be coded using the latest version of World Health Organization (WHO) Drug Dictionary providing Anatomical Therapeutic Chemical (ATC) Level 2 and ATC Level 4 codes.

Prior medications are defined as medications that started and stopped prior to the date/time of first CCI infusion.

Concomitant medications are defined as medications that start on or after the date/time of first CCI infusion or starts before and is ongoing on the date of first CCI infusion until the end of the study.

Prior medications will be summarized in a frequency table with the number and percentage of patients taking the specific prior medication. The frequency table will be presented by ATC Level 2, ATC Level 4 and by patient type and overall.

Concomitant medications/therapies will be summarized with the number and percentage of patients taking the specific medications. The summary table will be presented with ATC Level 2 and ATC Level 4 and by patient type and overall.

Listing of prior medications, concomitant medications/therapies will include ATC Level 2, ATC Level 4. These listings will be sorted by patient type, patient ID, chronological start date, ATC Level 2, ATC Level 4.

7 SPECIFIC ANALYSIS RULES

7.1 Definition of baseline, post-baseline, and other time points

Unless otherwise specified, baseline measurement is defined as the latest non-missing assessment prior to the first dose of CCI

All data will be collected at predefined timepoints according to protocol, unless otherwise deemed necessary.

Invalid laboratory data may not be used (from hemolyzed samples, mishandled samples, quantity not sufficient, or other conditions that would render values invalid). Unscheduled assessment (e.g., laboratory values, vital signs, or 12-lead ECG results associated with non-protocol clinical visits, obtained while investigating or managing AEs) will be included only in the listings.

If more than one value is reported for a given visit, the value closest to the scheduled visit will be selected in the summary, while all reported values will be included in the listings.

7.2 Visit windows

All data will be organised and analysed according to the scheduled visits outlined in the protocol. However, actual observation times may differ from the scheduled visit times and where this occurs the results should be allocated to the most appropriate visit.

The PO assessment timepoints will be assigned following protocol-specified visit windows. For example, assessment occurring 24±4 hours post-surgical wound closure will be assigned to the visit of 24 hours post-surgical wound closure. Similarly, assessment occurring 7±1 days from hospital discharge to last dose of CCI for peri-operative management will be assigned to the visit of 7 days from hospital discharge to last dose of CCI for peri-operative management.

All other analyses will use the visits and timepoints as reported in the eCRF. No further reassignment of the visits will be done.

7.2.1 Time windows for blood component transfusion and CCI administered

The amount of blood component transfusion (mL) and CCI administered (mg) will be derived based on the following time windows:

- IO period: from 24 hours prior to surgery until wound closure
- 24 hours PO period: from surgical wound closure until 24 hours post wound closure
- 120 hours PO period: from surgical wound closure until 120 hours post wound closure
- Day 6 PO period
- Day 7 PO period
- Day 8 PO period

- Day 9 PO period
- Day 10 PO period
- Day 11 PO period
- Day 12 PO period
- Day 13 PO period
- Day 14 PO period
- Day 15 PO period

The amount of CCI administered (mg) will also be derived based on the time windows as below:

During surgery and post-surgery:
- During Surgery: from 24 hours prior to surgery until wound closure
- Post-Surgery: from wound closure to last visit

By use:
- During surgery through D5: from 24 hours prior to surgery through D5
- All hospital stay: from surgical wound closure to hospital discharge
- At home: from hospital discharge to last visit

7.3 Definition of derived variables

7.3.1 Demography and other baseline characteristics

Data including age at informed consent, sex, race, ethnicity, height, weight will be reported/used as collected on the eCRF.

The following rules will be applied in variable derivation:
- Weight will be reported in kilograms (kg) and height will be reported in centimeter (cm)
- BMI (kg/m²):

$$BMI(Kg/m^2) = \frac{Weight(Kg)}{Height^2(m)}$$

The derived data will be listed.

7.3.2 Disposition

A patient will be considered to have completed the study if the patient has completed all visits of the study including the last visit (48±4 hours after last dose of CCI for peri-operative management or premature patient discontinuation) and received the phone call 28 ± 2 days after the last visit from investigator or designee. If the completion date is not recorded on the corresponding eCRF page, the latest scheduled clinic visit will be imputed as the completion date.

For patients who withdrew from the study and no date of discontinuation is collected, the date of discontinuation will be imputed as the date of the last attended scheduled study visit.

7.3.3 Durations

Study duration (years) is from date of informed consent/assent to EoS visit, i.e. [(Date of EoS) – (Date of informed consent/assent) +1]/365.25.

Treatment duration (days) is from the date of first dose to the date of last dose of CCI i.e. (Date of last dose) – (Date of first dose) +1.

Surgery duration (hours) is the duration from surgical incision start date/time to skin closure date/time, i.e., (skin closure date/time) – (surgical incision start date/time). This will be reported in HH:MM notation if the format reported in eCRF corresponding page is different.

Duration of ICU (days) is from the ICU admission date/time to the ICU discharge date/time, i.e., (ICU discharge date/time) – (ICU admission date/time).

Duration of hospitalization (days) is from the day of surgery until hospital discharge, i.e., (hospital discharge date) – (surgical incision start date) + 1.

7.4 Laboratory standardization

In this study, all test assessments will be performed at the local laboratories. Thus, laboratory results standardization will be applied.
In general, the transformed laboratory result will be derived using the expression:

$$R_T = S_L + \frac{R_U - I_L}{I_H - I_L}(S_H - S_L),$$

where R_U and R_T are the untransformed result and transformed result, respectively, and (I_L, I_H) and (S_L, S_H) are the investigators' and standard lower and upper limits of normality, respectively.

For details, please refer to the Local Lab Conventions for this study.

8 CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Changes made post SAP finalization will be documented in the section 9.8 of the CSR. An explanation will be provided for deviations from the planned analysis.

9 REFERENCES

1. Protocol LFB-FVIIa-008-14 Amendment 4 dated 20 December 2016, A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3).
2. Clopper, C., Pearson, E. S., (1934). The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika, 26: 404-413.

10 COMPUTER SYSTEM AND SOFTWARE

10.1.1 Computer system

The statistical analysis will be performed using Windows Server 2016 Standard.

10.1.2 Software

All tables, listings and figures will be produced and statistical analysis performed using SAS® version 9.4. All output will be in Microsoft Word Format.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.3. Pinnacle 21 Community Validator Engine Version 4.0.1.1 will be utilised to ensure compliance with CDISC standards.

Study Data Tabulation Model (SDTM) datasets will be prepared using CDISC Standard Version 1.7, and CDISC SDTM Implementation Guide Version 3.3.

11 STATISTICAL APPENDICES

The title of each generated table, figure, and listing should be bookmarked within the Microsoft Word document (one single bookmark per table/listing) to allow document publishing.

Footnotes should be used to clarify ambiguities (e.g., the denominator used to calculate a percentage). All footnotes for key symbols (*, ~) will be in the order that they appear in the display.

11.1.1 Tables

The numbering of the tables must be easily integrated in the CSR following the ICH E3 Section 14.

Tables will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size of 8 and according to the requirements for documents to be ready for submission.

All tables, in table number order, must be presented in a single Microsoft Word file.

11.1.2 Figures

Figures will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size as 8 and according to the standard margins.

11.1.3 Listings

Data listings are presented for all screened patients. The numbering of the listings must be easily integrated in the CSR following the ICH E3 Section 16.2.

Listings will be presented in landscape, in a fixed font (courier or SAS monospace) with a minimum size as 8 and according to the standard margins.

APPENDICES

Appendix 1: Global hemostatic response based on the individual scores during the intra-operative period and at 24 and 120 hours after surgical wound closure

Individual scores			Global hemostatic response score*	Global hemostatic response
Intra-operative	24 hours post-operative	120 hours post-operative		
3	3	3	7-9 (no individual score <2)	EXCELLENT
3	3	2		
3	2	3		
3	2	2		
2	3	3		
2	3	2		
2	2	3		
3	1	3	5-7 (no intra-operative and 120 hours post-operative individual score <2 and no 24 hours post-operative score <1)	GOOD
3	1	2		
2	2	2		
2	1	3		
2	1	2		
3	3	0 or M	5-6 (with one individual score = 0 or missing (without a replacement score) [M])	MODERATE
3	2	0 or M		
2	3	0 or M		
3	0 or M	3		
3	0 or M	2		
2	0 or M	3		
0 or M	3	3		
0 or M	3	2		
0 or M	2	3		
2	1	1	3-7 (no individual score <1)	
1	2	1		
1	1	2		
3	3	1		
3	2	1		
3	1	1		
2	2	1		
2	2	1		
1	3	3		
1	3	2		
1	3	1		
1	2	3		
1	2	2		
1	1	3		
1	1	1		
3	1	0 or M	0-4 (with at least one individual score = 0 or missing (without a replacement score) [M])	POOR
3	0 or M	1		
3	0 or M	0 or M		
2	2	0 or M		
2	0 or M	2		
2	1	0 or M		
2	0 or M	1		
1	3	0 or M		
1	0 or M	3		
1	2	0 or M		
1	0 or M	2		
0 or M	3	1		
0 or M	3	0 or M		
0 or M	2	2		
0 or M	2	1		

Individual scores			Global hemostatic response score*	Global hemostatic response
Intra-operative	24 hours post-operative	120 hours post-operative		
0 or M	1	3	0-4 (with at least one individual score = 0 or missing (without a replacement score) [M])	POOR
0 or M	1	2		
0 or M	0 or M	3		
2	0 or M	0 or M		
1	1	0 or M		
1	0 or M	1		
1	0 or M	0 or M		
0 or M	2	0 or M		
0 or M	1	1		
0 or M	1	0 or M		
0 or M	0 or M	2		
0 or M	0 or M	1		
0 or M	0 or M	0 or M		

Global hemostatic response score is the aggregate or sum of the non-missing component scores. A missing component score could be replace collected assigned score based on the rules indicated in protocol Section **Error! Reference source not found..*

Appendix 2: Imputation for missing or incomplete dates

All data listings will display missing or incomplete dates as reported without imputation.

Dates of historical events such as the date of diagnosis, date of onset, start/stop dates of previous treatment, start dates of medical conditions, etc. will be imputed when partial dates are collected. In case of missing month and day and available year YYYY the corresponding date will be replaced with "15JULYYYY". In case of missing day the date will be replaced with "01MMMYYYY".

The imputation method for the handling of missing or partial dates for adverse event (AE) and concomitant medication (CM) will be as follows:

Start Dates

- If the day is missing, this will be imputed as the first day of the month.
- If the month is missing, this will be imputed as JAN.
- If the year is missing, the event will be considered as a treatment-emergent adverse event/concomitant medication and no imputation of the date will occur.

Stop Dates

- If the day is missing this will be imputed as the last day of the month.
- If the month is missing this will be imputed as DEC.
- If the year is missing, the adverse event/medication will be considered as ongoing and no imputation of the date will occur.

An implementation example is given below:

Partial Start Date	Imputed Start Date	Partial Stop Date	Imputed Stop Date
--JUN2006	01JUN2006	--JUN2006	30JUN2006
26___2006	26JAN2006	26___2006	26DEC2006
01JUN___	No imputation[1]	01JUN___	No imputation[2]

[1]Adverse event (medication) will be considered as a treatment-emergent adverse event (concomitant medication).
[2]Adverse event/medication will be considered ongoing.

Appendix 3: List of laboratory tests

Hematology

- Hematocrit (Hct)
- Hemoglobin (Hb)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential (automated)
- CD4+ cell count[1]

Urinalysis (dipstick)

- Glucose
- Ketones
- Nitrite
- Occult blood
- Protein
- Microscopic examination of sediment in case of positive dipstick

Serology[1]

- Hepatitis B surface antigen (HbsAg)
- Hepatitis C virus (HCV)
- Human immunodeficiency virus (HIV)

Other[1]

- FVIII[2,4] or FIX[3] inhibitors

Serum Chemistry

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Total protein
- Troponin T

Coagulation

- FVIII[1,2,4] or FIX[1,3]
- Prothrombin time (PT)[1]
- Activated partial thromboplastintime (aPTT)[1,5]
- Fibrinogen
- D-dimer
- Prothrombin fragment F 1+2 (F 1+2)
- Antithrombin III (AT III)[6]

[1]*At Screening only*
[2]*In hemophilia A patients only*
[3]*In hemophilia B patients only*
[4]*Bovine chromogenic for emicizumab patients*
[5]*Only for patients without emicizumab*
[6]*At Screening only for patients with a history of treatment with fitusiran*

Appendix 4: Multiple imputation

Multiple imputation approach by Fully Conditional Specification (FCS) will be used to handle missing data with the assumption of missing at random (MAR).

Key covariates to be considered in the logistic model include patient type, Hemophilia type (if there are different types), hemophilia severity at screening, baseline hemoglobin level, baseline fibrinogen level, Factor VIII/IX level at baseline, Factor VIII/IX inhibitor status at baseline (BU≥5, or BU <5), estimated total blood loss (mL), blood product transfusion (Yes, No). Other covariates could be included if deemed relevant.

A stepwise logistic regression will be used to identify covariates to be included in the imputation by a backward elimination analysis based on iterative maximum likelihood with the Newton-Raphson algorithm with a significance level of 0.2.

The multiple imputation method consists of the following 3 steps:

Step 1: Imputation of missing values from the "imputation model" with the selected covariates repeated *m* (say 1000) times, which results in *m* completed imputed datasets under missing at random (MAR) framework. This step can be performed using SAS PROC MI with seed = 2202 and burn-in = 40.

Step 2: Calculating the proportion of successfully treated bleeding for each of *m* imputed datasets separately.

Step 3: Pooling of the *m* sets of estimates to obtain an overall set of estimate and corresponding standard error. This step can be performed using SAS PROC MIANALYZE. And the corresponding CI will be calculated based on the estimates and standard error.

Appendix 5: Display list table

This table includes, but not limits to, a list of displays to cover the analyses planned in this SAP. Any subsequent changes of the list will be reflected in the study TFL mock shells.

Display Type	Display Numbering	Display Population	Display Title	Note
Safety – Demographics and Medical History				
Table	14.1.1.1	All	Summary of Screened Patients by Patient Type and Overall	
Table	14.1.1.2	Enrolled	Disposition of Patients by Patient Type and Overall (Enrolled Patients)	
Table	14.1.1.3	SAF	Summary of Important Protocol Deviation by Patient Type and Overall (SAF)	
Table	14.1.2	SAF	Patient Demographics and Baseline Characteristics by Patient Type and Overall (SAF)	
Table	14.1.3.1	SAF	Medical History by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.1.3.2	SAF	Disease Characteristics by Patient Type and Overall (SAF)	
Table	14.1.4	SAF	Surgery Characteristics by Patient Type and Overall (SAF)	
Table	14.1.5	SAF	Prior Medications by Patient type and Overall (SAF)	
Table	14.1.6	SAF	Concomitant Medications by ATC Level 2 and Level 4, by Patient Type and Overall (SAF)	
Efficacy Table				
Table	14.2.1	FAS	Primary Analysis: Primary Efficacy Endpoint –Summary of Global Hemostatic Response Based on the Intra-operative Score and the Post-operative Scores at 24 and 120 Hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.1.1	FAS	Sensitivity Analysis 1: Primary Efficacy Endpoint –Summary of Global Hemostatic Response Based on the Intra-operative Score	

Display Type	Display Numbering	Display Population	Display Title	Note
			and the Post-operative Scores at 24 and 120 Hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.1.2	FAS	Sensitivity Analysis 2: Primary Efficacy Endpoint –Summary of Global Hemostatic Response Based on the Intra-operative Score and the Post-operative Scores at 24 and 120 Hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.1.3	PP	Primary Efficacy Endpoint –Summary of Global Hemostatic Response Based on the Intra-operative Scores and Post-operative Scores at 24 and 120 Hours After Surgical Wound Closure by Patient Type and Overall (PP)	PP analysis will be omitted if PP is 30% less than FAS.
Table	14.2.2	FAS	Secondary Endpoint – Summary of Hemostatic Response Assessment During the Intra-operative Period and at 24 and 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.2.1	PP	Secondary Endpoint – Summary of Hemostatic Response Assessment During the Intra-operative Period and at 24 and 120 hours After Surgical Wound Closure by Patient Type and Overall (PP)	PP analysis will be omitted if PP is 30% less than FAS
Table	14.2.3	FAS	Secondary Endpoint – Summary of Hemostatic Response Assessment at Each Timepoint post 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.3.1	PP	Secondary Endpoint – Summary of Hemostatic Response Assessment at Each Timepoint post 120 hours After Surgical Wound Closure by Patient Type and Overall (PP)	PP analysis will be omitted if PP is 30% less than FAS
Table	14.2.4	FAS	Secondary Endpoint – Summary of Intra-operative Blood Loss Determined by the Surgeon as Compared to the Surgeon's	

Display Type	Display Numbering	Display Population	Display Title	Note
			Maximum Predicted Blood Loss by Patient Type and Overall (FAS)	
Table	14.2.5	FAS	Secondary Endpoint – Summary of Post-operative Blood Loss Determined by the Investigator as Compared to the Investigator's Maximum Predicted Blood Loss at 24 and 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.6	FAS	Secondary Endpoint – Summary of Blood Product Transfusion as Compared to the Investigator's Maximum Predicated Blood Product Transfusion at Wound Closure, 24 and 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Table	14.2.7	FAS	Secondary Endpoint – Summary of CCI Administered per Surgery by Use During Surgery Through D5, in Hospital, at Home, or for Specific Reasons by Patient Type and Overall (FAS)	Includes Total and by use.
Table	14.2.8	FAS	Secondary Endpoint – Summary of Bleeding Episodes at the Surgical Site Between Surgical Wound Closure and Last Visit by Patient Type and Overall (FAS)	Add footnote to define "Last visit";
Table	14.2.9	FAS	Secondary Endpoint – Summary of Surgical Interventions/Re-explorations for Bleeding Episodes Between Surgical Wound Closure and Last Visit by Patient Type and Overall (FAS)	Add footnote to define "Last visit";
Table	14.2.10	FAS	Secondary Endpoint – Summary of Deaths from Start of Surgery to End of Study by Patient Type and Overall (FAS)	Add footnote to define "End of Study";
Table	14.2.11	FAS	Exploratory Endpoint – Summary of Duration in ICU and in Hospital From Day of Surgery Until Hospital Discharge by Patient Type and Overall (FAS)	

Display Type	Display Numbering	Display Population	Display Title	Note
Figure	14.2.1.1	FAS	Primary Efficacy Endpoint – Forest Plot of Global Hemostatic Response Based on the Intra-operative Score and the Post-operative Scores at 24 and 120 Hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Figure	14.2.2.1	FAS	Secondary Endpoint – Forest Plot of Hemostatic Response Assessment During the Intra-operative Period, at 24 and 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Figure	14.2.3.1	FAS	Secondary Endpoint – Forest Plot of Hemostatic Response Assessment at Each Timepoint post 120 hours After Surgical Wound Closure by Patient Type and Overall (FAS)	
Figure	14.2.4.1	FAS	Secondary Endpoint – Spaghetti Plot of Actual Blood Loss and Hemostatic Response Assessment Over Time by Patient (FAS)	
Figure	14.2.6.1	FAS	Secondary Endpoint – Spaghetti Plot of Blood Products Transfusion (mL) and Hemostatic Response Assessment Over Time by Patient (FAS)	
Figure	14.2.7.1	FAS	Secondary Endpoint – Spaghetti Plot of CCI Administered and Hemostatic Response Assessment Over Time by Patient (FAS)	
Safety - Exposure				
Table	14.3.1.1	SAF	Summary of Exposure to CCI by Patient Type and Overall (SAF)	
Safety – Adverse Event				
Table	14.3.2.1	SAF	Summary of All Adverse Events (AEs) by Patient Type and Overall (SAF)	
Table	14.3.2.2	SAF	Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	

Display Type	Display Numbering	Display Population	Display Title	Note
Table	14.3.2.3	SAF	Summary of Common (>=2 Patients) Treatment-Emergent Adverse Events (TEAEs) by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.4	SAF	Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA SOC and Preferred Term, by Severity, by Patient Type and Overall (SAF)	
Table	14.3.2.5	SAF	Summary of Treatment-Related Treatment-Emergent Adverse Events by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.6	SAF	Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA SOC and Preferred Term, by Outcome, by Patient Type and Overall (SAF)	
Table	14.3.2.7	SAF	Summary of Non-serious Treatment-Emergent Adverse Events (SAEs) by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.8	SAF	Summary of Treatment-Emergent Serious Adverse Events (TESAEs) by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.9	SAF	Summary of Treatment-Emergent Adverse Events (TEAEs) Leading to Study Discontinuation by MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.10.1	SAF	Summary of Treatment-Emergent Adverse Events of Special Interest (TEAESIs) by Patient Type and Overall (SAF)	
Table	14.3.2.10.2	SAF	Summary of Treatment-Emergent Adverse Events of Special Interest (TEAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	

Display Type	Display Numbering	Display Population	Display Title	Note
Table	14.3.2.10.3	SAF	Summary of Treatment-Related Treatment-Emergent Adverse Events of Special Interest (TEAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.10.4	SAF	Summary of Treatment-Emergent Adverse Events of Special Interest (TEAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Severity, by Patient Type and Overall (SAF)	
Table	14.3.2.10.5	SAF	Summary of Treatment-Emergent Adverse Events of Special Interest (TESAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Outcome, by Patient Type and Overall (SAF)	
Table	14.3.2.10.6	SAF	Summary of Non-serious Treatment-Emergent Adverse Events of Special Interest (TEAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.10.7	SAF	Summary of Treatment-Emergent Serious Adverse Events of Special Interest (TESAESIs) by AESI Category, MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Table	14.3.2.10.8	SAF	Summary of Treatment-Emergent Adverse Events of Special Interest (TEAESIs) Leading to Study Discontinuation by AESI Category, MedDRA SOC and Preferred Term, by Patient Type and Overall (SAF)	
Safety – Serum Chemistry				
Table	14.3.3.1.1	SAF	Summary of Serum Chemistry Values by Visit, by Patient Type and Overall (SAF)	Change from baseline is included
Table	14.3.3.1.2	SAF	Shift Table for Serum Chemistry Assessments by Visit, by Patient Type and Overall (SAF)	

Display Type	Display Numbering	Display Population	Display Title	Note
Table	14.3.3.1.3	SAF	Summary of Serum Chemistry Assessments by Categories, by Visit, by Patient Type and Overall (SAF)	
Safety – Hematology				
Table	14.3.3.2.1	SAF	Summary of Hematology Values by Visit, by Patient Type and Overall (SAF)	Change from baseline is included.
Table	14.3.3.2.2	SAF	Shift Table for Hematology Assessments by Visit, by Patient Type and Overall (SAF)	
Table	14.3.3.2.3	SAF	Summary of Hematology Assessments by Categories, by Visit, by Patient Type and Overall (SAF)	
Figure	14.3.3.2.4	FAS	Spaghetti Plot of Hemoglobin Levels and Hemostatic Response Assessment Over Time by Patient (FAS)	
Safety – Coagulation				
Table	14.3.3.3.1	SAF	Summary of Coagulation Values by Visit, by Patient Type and Overall (SAF)	Change from baseline is included
Table	14.3.3.3.2	SAF	Shift Table for Coagulation Assessments by Patient Type and Overall (SAF)	
Table	14.3.3.3.3	SAF	Summary of Coagulation Assessments by Categories, by Visit, by Patient Type and Overall (SAF)	
Safety – Urinalysis				
Table	14.3.3.4.1	SAF	Summary of Urinalysis Data by Visit, by Patient Type and Overall (SAF)	
Table	14.3.3.4.2	SAF	Shift Table for Urinalysis Data by Visit, by Patient Type and Overall (SAF)	
Table	14.3.3.4.3	SAF	Summary of Urinalysis Data by Categories, by Visit, by Patient Type and Overall (SAF)	

Display Type	Display Numbering	Display Population	Display Title	Note
Safety – Serology				
Table	14.3.3.5.1	SAF	Summary of Serology Assessment at Baseline by Patient Type and Overall (SAF)	
Safety – Vital Signs				
Table	14.3.4.1	SAF	Summary of Vital Signs by Visit, by Patient Type and Overall (SAF)	Change from baseline is included
Table	14.3.4.2	SAF	Shift Table for Vital Signs Data by Visit, by Patient Type and Overall (SAF)	
Table	14.3.4.3	SAF	Summary of Vital Signs by Categories, by Visit, by Patient Type and Overall (SAF)	
Safety – ECG				
Table	14.3.5.1	SAF	Summary of 12-ECG Assessment at Baseline by Patient Type and Overall (SAF)	
Safety – Physical Exam				
Table	14.3.6.1	SAF	Summary of Physical Examination by Body System, by Visit, by Patient Type and Overall (SAF)	
Table	14.3.6.2	SAF	Shift Table for Physical Examination by Body System, by Visit, by Patient Type and Overall (SAF)	
All Listings				
Listing	16.2.1.1	All	Screened Failures	
Listing	16.2.1.2	Enrolled	Patient Disposition – Enrolled Patients	
Listing	16.2.2	SAF	Protocol Deviations – SAF	
Listing	16.2.3	SAF	Patients Excluded from the Efficacy Analysis – SAF	
Listing	16.2.4.1	SAF	Demographics and Baseline Characteristics – SAF	
Listing	16.2.4.2	SAF	Medical History – SAF	

Display Type	Display Numbering	Display Population	Display Title	Note
Listing	16.2.4.3	SAF	Disease Characteristics – SAF	
Listing	16.2.4.4	SAF	Surgical or Invasive Procedure Characteristics – SAF	
Listing	16.2.4.5	SAF	Surgical/Therapeutic Procedures – SAF	
Listing	16.2.4.6	SAF	Prior and Concomitant Medications – SAF	
Listing	16.2.4.7	SAF	ICU Admission and Discharge – SAF	
Listing	16.2.4.8	SAF	Bleeding Episodes – SAF	
Listing	16.2.4.9	SAF	Blood Transfusion – SAF	
Listing	16.2.4.10	SAF	Rescue Therapy – SAF	
Listing	16.2.5	SAF	Study Drug Administration – SAF	
Listing	16.2.6	SAF	In-operative and Post-operative Hemostatic Response Assessments – SAF	
Listing	16.2.7.1	SAF	Adverse Events– SAF	
Listing	16.2.7.2	SAF	Adverse Events leading to Death – SAF	
Listing	16.2.7.3	SAF	Adverse Events leading to Study Discontinuation – SAF	
Listing	16.2.7.4	SAF	Serious Adverse Events – SAF	
Listing	16.2.7.5	SAF	Adverse Events of Special Interest (AESIs) – SAF	
Listing	16.2.7.6	SAF	Death – SAF	
Listing	16.2.8.1	SAF	Laboratory Data: Hematology – SAF	
Listing	16.2.8.2	SAF	Laboratory Data: Coagulation – SAF	
Listing	16.2.8.3	SAF	Laboratory Data: Serum Chemistry – SAF	
Listing	16.2.8.4	SAF	Laboratory Data: Urinalysis – SAF	
Listing	16.2.8.5	SAF	Laboratory Data: Serology – SAF	
Listing	16.2.9	SAF	Vital Signs – SAF	
Listing	16.2.10	SAF	12-Lead ECG – SAF	
Listing	16.2.11	SAF	Physical Examination – SAF	