CLINICAL STUDY PROTOCOL F7TG2202

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

SHORT TITLE: SCOPE HIM

Phase 3

VERSION FINAL 3.0 – 03 April 2025

included amendments No.1 v 1.0 – 24 July 2023 & No.2 v 1.0 – 03 April 2025

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	amino acid
ADAs	antidrug antibodies
AE	adverse event
AESIs	adverse events of special interest
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
AT III	antithrombin III
ATC	Anatomical Therapeutic Chemical
BU	Bethesda units
BUN	blood urea nitrogen
°C	degrees Celsius
Ca	calcium
CBC	complete blood count
CHMP	Committee for Medicinal Products for Human Use
CI(s)	confidence interval(s)
CMO	contract manufacturing organization
COVID	Coronavirus Disease
CRO	contract research organization
CT	computed tomography
D1	Day 1 (i.e. 24 ± 4 hours post-surgical wound closure)
D15	Day 15
D5	Day 5 (i.e. 120 ± 4 hours post-surgical wound closure)
dL	deciliter
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
ECG	electrocardiogram
eCRF	electronic case report form
EGF	epidermal growth factor
EMA	European Medicines Agency
EU	European Union
°F	degrees Fahrenheit
FAS	full analysis set
FDA	Food and Drug Administration
FEIBA®	factor eight inhibitor bypassing agent
FIX	factor IX

FVII	factor VII
FVIIa	activated factor VII
FVIII	factor VIII
FVIIIa	activated factor VIII
FX	factor X
FXa	activated factor X
GCP	good clinical practice
GPV	Global PharmacoVigilance
h	hours
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLGT	High-level group term
HLT	High-level term
HTRS	Hemophilia and Thrombosis Research Society
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IFU	instruction for use
IMP	investigational medicinal product
IO	intra-operative
IRB	institutional review board
IRS	interactive response system
ITI	immune tolerance induction
IV	intravenous
K	potassium
kDa	kilodalton
kg	kilogram
LDH	lactate dehydrogenase
LFB	Laboratoire Français du fractionnement et des Biotechnologies
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
µL	microliter
mL	milliliter
MRI	magnetic resonance imaging
Na	sodium
NEC	not elsewhere classified
NSAIDS	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PCC	prothrombin complex concentrate
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PE	pulmonary embolism

Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetic(s)
PO	post-operative
PP	per protocol
PT	prothrombin time (in MedDRA)
PT	preferred term (in laboratory tests)
RBC	red blood cell (count)
rFVIII	recombinant coagulation factor VIII
rhFVII	recombinant human factor VII
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SI	international system of units
SmPC	summary of product characteristics
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
TEAEs	treatment-emergent adverse events
TEAESIs	treatment-emergent adverse events of special interest
TESAEs	treatment-emergent serious adverse events
TF	tissue factor
TXA	tranexamic acid
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	white blood cell (count)
WFH	World Federation of Hemophilia
WFI	water for injection
WHODrug	World Health Organization Drug

DEFINITIONS FOR THE SPECIFIC PURPOSE OF STUDY F7TG2202

Major surgical procedure (adapted from Santagostino et al., 2015 [1])	An invasive operative procedure where one or more of the following occurred: • a body cavity was entered; • a mesenchymal barrier was crossed; • a fascial plane was opened; • an organ was removed; • normal anatomy was operatively altered. Multiple simultaneous dental extractions (at least 3) included [2]. Expected duration of surgery-related rFVIIa treatment: at least 5 days, including the day of surgery. Brain procedures, single or double dental extraction and port placement/removal, which may sometimes be considered major procedures are excluded. By contrast, minor surgeries are defined as invasive operative procedures in which only skin, mucous membranes, or superficial connective tissue are to be manipulated. Expected duration of surgery-related rFVIIa treatment in minor surgeries is less than 5 days, including the day of surgery.
IMP	LFB's recombinant human FVIIa, called CCI
IMP extradose	An individual dose of CCI either >75 µg/kg (+10%) (except the pre-surgical dose) or within <2 hours (-15 minutes) of the prior dose ordered by the treating physician, with the intent of stopping or controlling a bleed related to the surgery, except in cases specifically permitted (e.g. before tourniquet, drain or suture removal, or prior to physical therapy session)
T0	This timepoint will correspond to the wound closure
IO period	Period from surgical incision until wound closure
24-hour PO period	Period from surgical wound closure until 24 hours post wound closure (i.e. from 0 to 24 hours)
120-hour PO period	Period from surgical wound closure until 120 hours post wound closure (i.e. from 0 to 120 hours)
Last CCI dose for peri-operative management	Last dose of CCI required for the bleeding management associated to surgery excluding any dose only used as a bleeding prevention treatment associated to physical therapy The last dose of CCI will be defined by investigator on ongoing basis according to the evolution of the patient's hemostasis.

INVESTIGATOR'S AGREEMENT

Investigator Agreement and Signature:

I have read and agree to Protocol F7TG2202 entitled "A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Patients with Congenital Hemophilia A or B with Inhibitors to Factor VIII or IX Undergoing Elective Major Surgical Procedures'' with Amendments No.1 and No.2. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: [ ]
TITLE: [PRINCIPAL] INVESTIGATOR SIGNATURE:

DATE:
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COORDINATING INVESTIGATOR'S AGREEMENT

Coordinating Investigator Agreement and Signature:

I have read and agree to Protocol F7TG2202 entitled "A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Patients with Congenital Hemophilia A or B with Inhibitors to Factor VIII or IX Undergoing Elective Major Surgical Procedures'' with Amendments No.1 and No.2. I am aware of my responsibilities as a coordinating investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME: PPD
TITLE: COORDINATING INVESTIGATOR

SIGNATURE: PPD

DATE: 03-Apr-2025
OFFICE: PPD
PPD

SUMMARY OF CHANGES

The current version of the protocol was released on 03 April 2025 and included in Section 11.12 - Protocol Amendment History.

Amendment	Released Date	Protocol Version Number
1	**24 July 2023**	**2.0**
2	**03 April 2025**	**3.0**

1. PROTOCOL SUMMARY

1.1. Synopsis

TITLE	A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Patients with Congenital Hemophilia A or B with Inhibitors to Factor VIII or IX Undergoing Elective Major Surgical Procedures Short title: SCOPE HIM
STUDY SUMMARY	This is an interventional, prospective, international, multicenter, single-arm, Phase 3, and sequential efficacy and safety study in adolescents and adults with congenital hemophilia A or B with inhibitors to factor VIII (FVIII) or factor IX (FIX) undergoing elective major surgical procedures. After informed consent/assent signatures, the study will proceed into 3 periods (i.e. screening period, treatment period starting before, and ending days after the planned surgery, and follow-up period). The screening period will be done within one month before surgery (Days -28 to Day -1) to check eligibility criteria. Patients meeting all eligibility criteria will undergo the planned surgery. Then, the patient will receive intravenously the first CCI dose prior to surgery. The initial CCI dose of 200 µg/kg will be followed by repeated administration of doses of 75 µg/kg of CCI to manage bleeding associated to surgery according to the investigator's judgment and the dosing guidelines specified. The patient will be treated in hospital for at least 5 days. If the patient needs further treatment with CCI after hospital discharge, the patient will self-administer CCI at home. Then, there will be a follow-up period starting with a last visit 48 ± 4 hours after the last dose of CCI for peri-operative management until a follow-up phone call (i.e. end of study) 28 ± 2 days after the last visit. Safety assessment and use of concomitant medications (including transfusions if any) will be assessed throughout the study. Statistical hypothesis will be tested in this study. The main null hypothesis to be tested for the proportion of successfully treated major procedures [i.e. defined by a good or excellent global hemostatic response based on assigned scores from a defined 4-point hemostatic scale during the intra-operative (IO) period and, at 24 hours and 120 hours after surgical wound closure] is that the proportion is less than 0.55 against the alternative hypothesis that the proportion is at least 0.55.
OBJECTIVES	Primary objective: The primary objective of this study is 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. Secondary objective: The secondary objective of this study is to assess the safety of CCI
ENDPOINTS	Primary endpoint: The primary efficacy endpoint is the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response. 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) 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-

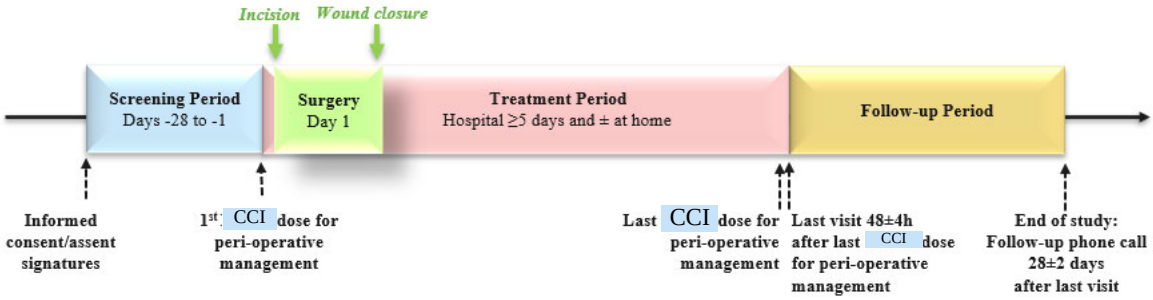
	hour PO period, i.e. 0-120 hours). The 4-point hemostatic scale rating and score assignments are provided by the surgeon at wound closure and by the investigator or designee at 24 and 120 hours after surgical wound closure. Secondary endpoints: • Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale at each of the following assessment timepoints: during the IO period, 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) • Proportion of successfully treated major procedures defined by a good or excellent global hemostatic response based on the 4-point hemostatic scale 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: at 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e. 0-24 hours period) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours) • 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 period) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours) • Mean change in hemoglobin (Hb) level from initiation of the surgery until last visit • 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 stay, 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 interventions/re-explorations for bleeding episodes between surgical wound closure and last visit • Number of deaths from bleeding attributed to ineffective hemostasis • 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 AEs 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 [fibrinogen and D-dimer levels] <u>Exploratory endpoint</u>: 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.
POPULATION	Population will be male patients aged ≥12 to ≤65 years with congenital hemophilia A or B with inhibitors to FVIII or FIX undergoing elective major surgical procedures. Subjects will be eligible regardless of whether they are using or not Emicizumab prophylaxis and/or bypassing agents. It is anticipated that a total of 22 patients will be screened. A total of 19 patients are planned to be enrolled to have a minimum of 17 evaluable elective major surgical procedures. No more than 1 major surgical procedure per patient will be approved for inclusion in the study.
PHASE	3
NUMBER OF SITES	More or less 18 sites as determined by a feasibility study
DESCRIPTION OF IMP	CCI lyophilized powder in single-use vials containing 5 mg of coagulation factor VIIa (recombinant)-jncw for intravenous (IV) infusion. The initial dose of CCI (200 µg/kg) will be followed for the IO period and the first 72 hours post-surgical wound closure by repeated administration of IV bolus doses of 75 µg/kg of CCI infused within ≤2 minutes every 2 hours ±15 minutes. Then, the frequency of CCI administration could be reduced by the investigator according to the dosing guidelines in this protocol. The minimum duration of CCI treatment will be 5 days at hospital.
STUDY DURATION	The study duration from first patient in to last patient in is estimated at 25 months.
PARTICIPANT DURATION	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.

1.2. Schema

The study schema is presented in Figure 1–1.

Figure 1–1: Study schema



After informed consent/assent signatures, the study will proceed into 3 periods (i.e. screening period, treatment period starting before, and ending days after the planned surgery, and follow-up period). The screening period will be done within one month before surgery (Days -28 to Day -1) to check eligibility criteria. Patients meeting all eligibility criteria will be enrolled in the study. Then, the patient will receive intravenously the first CCI dose prior to surgery. The initial CCI dose of 200 µg/kg will be followed by repeated administration of doses of 75 µg/kg of CCI to manage bleeding associated to surgery according to the investigator's judgment and the dosing guidelines specified in Table 7–2. The patient will be treated in hospital for at least 5 days. If the patient needs further treatment with CCI after hospital discharge, the patient will self-administer CCI at home. The last dose of CCI will be defined by investigator on ongoing basis according to the evolution of the patient's hemostasis. Then, there will be a follow-up period starting with a last visit 48 ± 4 hours after the last dose of CCI for peri-operative management until a follow-up phone call (i.e. end of study) 28 ± 2 days after the last visit.

Further details on study periods and visits are provided in Section 5.1 and Figure 5–1.

1.3. Schedule of Activities

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

Table 1–1: 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	
• 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							

	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**
Coagulation:								
• FVIII[12, 14] or FIX[13], PT, aPTT	X							
• ATIII	X[16]							
• Fibrinogen, D-dimer	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								
• 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				

	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**
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	
Transfusion (if any)[11]		X						

Legends of Table 1-1

Abbreviations: aPTT, activated partial thromboplastin time; AT III, antithrombin III; D15, Day 15; ECG, electrocardiogram; 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 Table 7–2.*
3. *Surgical procedure characteristics: Predicted surgery characteristics to complete as per requirements in Section 9.1.1. 3, 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*

2. KEY ROLES

Coordinating Investigator

The coordinating investigator is PPD

Sponsor's study team

The members of the sponsor's study team at the time the study is in an active recruitment phase are:

- Medical monitors
  PPD
- Clinical project manager
  PPD

The location of the LFB office is:

LFB BIOTECHNOLOGIES
3, avenue des Tropiques
BP 40305
91958 COURTABOEUF CEDEX
FRANCE

Clinical research organization (CRO)

The monitoring of study sites and the management of regulatory and biometry activities is subcontracted to an international CRO.

Contract manufacturing organization (CMO)

The IMP and administration kit labeling, packaging, storage, and logistics is subcontracted to a CMO.

Data monitoring committee (DMC)

An external DMC is set-up for this study. A charter defines the operational scope, including the frequency of meetings and function of the DMC. The DMC has two primary responsibilities:

1. The DMC will review the results of the planned interim analysis 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. For further details, please refer to Section 10.4.6.

3. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1. Study Rationale

Despite advances in prophylactic treatments for inhibitor patients, bypassing agents remain a necessity for the achievement of hemostasis in major surgical procedures. As such, this study F7TG2202 will collect safety and efficacy data to support the registration of a new bypassing agent (LFB's recombinant human FVIIa [CCI for the peri-operative management of adolescents (age ≥12 years) and adults with hemophilia A or B with inhibitors.

Specifically, the study will evaluate CCI for the achievement and maintenance of hemostasis in congenital hemophilia A or B patients who: 1) have inhibitors [Bethesda unit (BU) ≥5] or a known high anamnestic response or refractory to increased dosing of either FVIII or FIX (detailed history for these patients will be obtained to document the high-responding characteristics of their inhibitors); 2) are aged 12 to 65 years, inclusive; and 3) are undergoing elective major surgical procedures. Administration of CCI will be performed immediately prior to the initial surgical incision and will be repeated both intra- and post-operatively to achieve and maintain adequate hemostasis as determined by the investigator's judgment. Subjects will be eligible regardless of whether they are using or not emicizumab prophylaxis and/or bypassing agents.

3.2. Background Information

3.2.1. Congenital hemophilia, inhibitors and treatments

Hemophilia is an X-linked inherited coagulation disorder that results from reduced functional activity of FVIII (hemophilia A) or FIX (hemophilia B); the disease predominantly affects males. The global prevalence (estimated from registry data in countries with effective surveillance programs) is approximately 17/100,000 males (hemophilia A) and 4/100,000 males (hemophilia B) (WFH, survey 2020[3]). The disease is characterized by uncontrolled spontaneous and traumatic bleeding, with most bleeding occurring in joints. Repeated bleeding into the joint results in destruction of the cartilage by iron deposition, lysosomal enzymes and proinflammatory cytokines; this in turns leads to hemophilic arthropathy, joint destruction, and chronic disability – for which the only long-term solution is orthopedic surgery.

The standard of care for treatment of individuals with hemophilia is the replacement of the deficient coagulation factor (i.e. FVIII or FIX), either prophylactically or on-demand for the treatment of bleeding. Approximately 30% of people with hemophilia A and 5% of people with hemophilia B will develop antibodies (inhibitors) to the exogenous coagulation factor during their lifetime; the prevalence of inhibitor patients is estimated to be 5-8% of all hemophilia patients. Regardless of the severity of hemophilia, once an inhibitor develops, the outcome is the same: the bleeding phenotype worsens, morbidity and mortality increase, and (except in the case of low titer inhibitors) FVIII and FIX become ineffective treatment options. In these patients, bypassing agents are required to treat bleeding. In most countries, two classes of bypassing agents are approved for use: recombinant FVIIa [rFVIIa, NOVOSEVEN® RT, and in the United States (US), SEVENFACT® in adolescent and adult patients] and activated prothrombin complex concentrate (aPCC, FEIBA®). rFVIIa increases thrombin generation and drives coagulation by interacting with tissue factor, activated platelets, and (in vitro studies) the endothelial protein C receptor; aPCC supplies multiple activated and inactivated factor products to support coagulation by a multifaceted approach. Both classes of bypassing agent have

been shown to be effective in supporting hemostasis; however, historical data show that both can have unpredictable efficacy, and patient responsiveness can wax and wane.

Emicizumab, a bispecific antibody that mimics the functional role of FVIIIa, was approved for prophylactic use in inhibitor patients in 2017 (Genentech, Hemlibra, 2021[4]). Although emicizumab can significantly reduce the incidence of bleeding episodes, it cannot supply adequate hemostatic coverage to stop a bleed once bleeding has started (National Hemophilia Foundation Medical and Scientific Advisory Council, 2019[5]); for this, a bypassing agent (specifically rFVIIa, as aPCC is known to increase the risk of thromboembolic events in combination with emicizumab) is required. Thus, even in the era of novel prophylactic agents and a reduced frequency of bleeding, rFVIIa is still required by patients to control active bleeding.

3.2.2. Surgical procedures in inhibitor patients

Surgery in inhibitor patients is challenging, although the potential health-related quality of life improvements for the patient are substantial. In the absence of bypassing agents, strong efforts are required to prevent exsanguination; even when bypassing agents are utilized, bleeding complications are common (Erturan et al., 2019[6]; Kleiboer et al., 2021[7]). This is partly due to the inability of bypassing agents to support hemostasis as effectively as replacement FVIII or FIX; the known variability in patient response; wide variations in procedure type; surgeon inexperience with inhibitor patients; and the lack of validated lab assays to directly monitor coagulation status. As such, major procedures (i.e. those requiring at least 5 days of post-operative hemostatic coverage) are relatively rare in the inhibitor patient population and there is a lack of national guidelines that provide directions to support optimal outcomes across a range of procedures. In addition to orthopedic procedures resulting from hemophilic arthropathy, the increased life expectancy of hemophilia patients means that surgeries associated with disease and the normal aging process will become more common.

Two prospective, controlled surgical clinical studies with rFVIIa (NOVOSEVEN®) demonstrated the feasibility of rFVIIa use during major surgical procedures in inhibitor patients. Shapiro et al reported the use of repeat 35 µg/kg or 90 µg/kg bolus doses, with the 90 µg/kg dose regimen having a lower hemostatic failure rate in major procedures (Shapiro et al, 1998[8]). Studies have since shown that higher initial rFVIIa doses can be used to optimize the dosing regimen (Castaman, 2017[9]). Likewise, experience has shown rFVIIa coverage must be provided for an extended period of time post-operatively (sometimes weeks, depending on the patient and/or procedure) to prevent rebleeding and support physical therapy; a gradual increase in dosing interval is recommended. Pruthi et al demonstrated the comparability of continuous infusion and repeated 90 µg/kg bolus doses in major surgical procedures (Pruthi et al., 2007[10]). Subsequent experience has questioned the efficacy of continuous infusion (Giangrande et al., 2009[11]); as such, bolus infusion is the more common route of administration today.

Historically, antifibrinolytic agents [e.g. tranexamic acid (TXA) and aminocaproic acid] were not recommended for use in combination with rFVIIa due to concerns over thromboembolic events; that theoretical concern has since been demonstrated to be unfounded, and now national guidelines and expert opinion support the concomitant use of rFVIIa and antifibrinolytic agents, particularly in surgical procedures. Antifibrinolytic agents cannot initiate hemostasis; as such, they are ineffective in the absence of bypassing agents (Hedner et al. 1983[12]; Srivastava et al., 2020[13]).

Today, antifibrinolytic agents are frequently administered with rFVIIa during major surgical procedures in inhibitor patients; they are considered the standard-of-care by many surgeons and practitioners, although there is variability in their use (Escobar et al., 2012[14]; Escobar et al.,

2018[15]; Takedani et al., 2010[16]). Current World Federation of Hemophilia (WFH) guidelines support the concomitant use of antifibrinolytics in surgical procedures (Srivastava et al., 2020[13]). The MOSH study demonstrated that the non-use of adjunctive antifibrinolytic medication was associated with increased odds of major peri-operative bleeding in inhibitor patients (Kleiboer et al., 2021[7]). Furthermore, there is ample literature precedent to support their adjunctive use with bypassing agents in inhibitor patients undergoing major surgical procedures (Kleiboer et al., 2021[7]; Srivastava et al., 2020[13]; Kulkarni, 2013[17]; Bossard et al., 2008[18]; Takedani et al., 2015[19]; National Hemophilia Foundation Medical and Scientific Advisory Council, document 263[20]).

Current best practices for major procedures in inhibitor patients include (Castaman, 2017[9]; Giangrande et al., 2009[11]):

- High initial rFVIIa dose immediately prior to the procedure
- Aggressive rFVIIa dosing (e.g. every 2 hours) for the first several days following wound closure
- Gradual increase in rFVIIa dosing interval over multiple days/weeks
- Concomitant use of antifibrinolytic agents
- rFVIIa coverage for physical therapy

The approval and use of emicizumab has not altered the requirement for rFVIIa use during major procedures in inhibitor patients (Seaman et al., 2019[21]; National Hemophilia Foundation Medical and Scientific Advisory Council, document 258[22]). Due to the absence of prospective surgical clinical studies in inhibitor patients using emicizumab and the limited number of case studies/series reported in the literature, there is little guidance on how to optimally perform major procedures in this patient population and national guidelines are mostly silent, other than noting the absolute requirement for rFVIIa use. Expert opinion recommendations were reported by Jiménez-Yuste et al., 2021 [23] these note the continued frequent administration of rFVIIa for the first few days following wound closure; the gradual increase in rFVIIa dosing interval over multiple days and the use of concomitant antifibrinolytic agents. These recommendations are markedly similar to those for patients not using emicizumab, an observation rooted in the fact that emicizumab on its own cannot provide sufficient hemostatic coverage to stop ongoing bleeding (either acute or surgical). Thus, it should be expected that the intraoperative and first several days of post-operative hemostatic care for patients on emicizumab should be largely the same as for patients not using emicizumab.

3.2.3. CCI and completed clinical studies

LFB is developing a recombinant human FVIIa (CCI protein produced in and purified from the milk of transgenic rabbits, selected for the production of this complex human glycoprotein.

CCI is produced by recombinant deoxyribonucleic acid (DNA) technology employing site-directed expression of the human FVII gene in the mammary gland of genetically engineered rabbits. The transgene containing the human FVII has been stably integrated into the genome of the rabbits. The rhFVII gene is exclusively expressed by the mammary gland under the control of a beta-casein specific promoter. Milk from these transgenic rabbits is collected and the FVII protein expressed is subsequently purified and activated during the purification process. The production of recombinant human FVII in transgenic rabbits offers certain economic advantages over production of the protein in other genetically engineered cells, such as Baby Hamster Kidney and/or Chinese Hamster Ovary cells.

CCI is a recombinant human coagulation FVIIa of the vitamin K dependent family of coagulation factors. In the presence of both calcium and phospholipids, FVII/FVIIa in a complex with TF can

activate FX to FXa directly bypassing FIX or FVIII. Activation of FX to FXa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin and then converts fibrinogen to fibrin. FVIIa can bind directly to activated platelets at a site of vascular injury and activate other clotting factors to induce a thrombin burst necessary to form a fibrin clot.

FVIIa is a 406 amino acid (AA) glycoprotein (~50 kDa) with 12 disulfide bridges. The protein contains 4 distinct structural domains: the N-terminal γ-carboxylic-domain (gamma-carboxyglutamic acid-rich-domain), 2 epidermal growth factor (EGF)-like domains, and 1 serine protease domain. Activation of FVII to FVIIa results in the cleavage of the peptide bond Arg152-Ile153 generating an N-terminal Light Chain of 152 AA and a C-terminal Heavy Chain of 254 AA connected by a single disulfide bridge (Cys135-Cys262).

The clinical development has been designed to support registration of CCI for the on-demand treatment of bleeding episodes and for the achievement and maintenance of hemostasis in surgical interventions or other invasive procedures in congenital hemophilia A or B patients with inhibitors. The population foreseen is both adults and children (≥6 months of age to ≤75 years of age).

Efficacy and safety results from a previous Phase 3 study (PERSEPT 3) in congenital hemophilia A or B patients with inhibitors who underwent elective minor, or major surgical or other invasive procedure aged 6 months to 75 years provide the basis for the current study. The available results of this study and of additional completed studies [a Phase 1b and two other Phase 3 (PERSEPT 1 and PERSEPT 2) and a pharmacokinetic (PK)-oriented Phase 1 (Study LFB-FVIIA-009-19)] are more extensively described in the current CCI Investigator's Brochure (IB).

3.3. Risk/Benefit Assessment

3.3.1. Known potential risks

Important potential risks (since it has not been reported in clinical studies with eptacog beta while observed during clinical studies conducted with eptacog alpha) that are known to be associated with treatment with rFVIIa include hypersensitivity reactions, thromboembolic events (including in case of drug-drug interaction with bypassing agents or other hemostatic agents), and immunogenicity.

Hypersensitivity reactions:

The occurrence of an allergic or anaphylactic-type reaction has been identified as a real risk associated with the administration of CCI As recombinant coagulation FVIIa are produced by animal cells, the final product may indeed contain trace amounts of antibodies and other animal residual proteins. In addition, since CCI is produced in and purified from the milk of transgenic rabbits, immunogenic reaction either to CCI or to the rabbit milk protein may arise. Hypersensitivity reactions have been described with biological medicinal products from the same therapeutic class as CCI with a frequency estimated to be "rare" (≥1/10,000 to <1/1,000). Though no hypersensitivity reactions have been reported in previous CCI trials, such adverse effect cannot be totally ruled out.

Arterial and/or venous thrombotic events:

Though no thromboembolic events have been observed in CCI studies, based on the company experience with similar medicinal products, this risk is expected, with an "uncommon" frequency for the venous events and "rare" for the arterial ones [Novoseven® RT EU summary of product characteristics (SmPC)]. Clinical experience suggests that the risk of thrombotic events in hemophilia

patients treated with rFVIIa is low and is in many cases associated with pre-existing risk factors. A recent update of the clinical safety of rFVIIa over the last 20 years reported 249 thrombotic adverse events (AEs) in 217 individuals for the 5 million standard doses used (Neufeld et al., 2018[24]). Another recent analysis which reviewed safety data of Novoseven® in clinical studies, registries, and in post marketing surveillance, showed that thrombotic events in approved indications were rare, and that the specific risk factor for congenital hemophilia with inhibitors was 0.11%. The analysis also showed that an age above 65 years was the most common risk factor associated with thrombotic events (29%), alongside concomitant cardiac or vascular disease (18%). Other identified factors were use of aPCC (18%) (Rajpurkar et al., 2019[25]), and (non-factor medicinal products + bypassing agents) combinations (Linari et al. 2020[26]; Oldenburg et al., 2017[27]).

Immunogenicity:

Immunogenicity is a theoretical important risk factor for patients who may develop antibodies to any protein-based therapeutic. However, the possibility of immunogenicity is much less of a concern with rFVIIa, which is not a neoantigen in patients with hemophilia A or B who have a genetic disorder leading to either reduced production or a defective form of FVIII (for Type A) or FIX (for Type B) but not in FVII. No immune responses with inhibiting antibody to FVII formation have been observed in CCI studies. Nevertheless, neutralizing antibodies may occur. For further details, please refer to CCI IB.

3.3.2. Known potential benefits

Prior to the discovery and development of bypassing agents, elective major surgery was rarely performed in hemophilia patients with inhibitors because of the risk of uncontrollable bleedings and associated complications and deferred to the detriment of affected patients. With the availability of bypassing agents, despite remaining risks, surgery is now feasible in this population. However, bleeding complications are common, use of rescue therapy is sometimes required, and only two treatments are available in the US.

CCI would offer a novel treatment option in the control of surgical bleeding as some patients may be more optimally controlled on CCI In these patients, the treatment may also improve rehabilitation, decrease inpatient time, offer cost savings and improve health-related quality of life (better mobility, relief of chronic pain…) assuming bleeding complications can be avoided. In patients that may still receive first line treatment with other available therapeutic options, the introduction of CCI for peri-operative use could also offer a novel rescue option should complications arise. In the limited physician armamentarium for this rare and complex group of patients, CCI will be an additional drug to consider.

3.3.3. Assessment of potential risks and benefits

In conclusion, previous clinical studies have demonstrated that CCI is an effective and safe therapy for the treatment of bleeding episodes in patients (≥12 years of age) with hemophilia A and B with inhibitors. The risks associated with the use of CCI are consistent with those expected for this type of product. The benefits outweigh the risks and the overall risk-benefit ratio for CCI is considered positive in adults and adolescents.

3.3.4. Risk mitigation

To mitigate potential risks, though anti-rabbit milk proteins immunogenicity results from previous PERSEPT studies were supportive, patients with any of the following:

- Hypersensitivity to the active substance or to any of the excipients, or to rabbits or rabbit proteins
- Higher risk of thromboembolic events
- Platelet count below 100,000/µL
- Severe comorbidity, such as liver and/or renal impairment, active malignancy, or immunosuppression

will be excluded from the study.

The patient will also be thoroughly evaluated from the initial administration onwards to detect post-allergic symptoms which may consist of, but are not limited to:

- Skin redness, rash, hives
- Mucosal and/or skin swelling
- Difficulty breathing
- Hypotension
- Dizziness
- Nausea

Should such reaction arise, the surgeon in the operating room, the investigator during hospitalization and patients after hospital discharge should discontinue treatment and seek immediate medical attention, and subsequent treatment with CCI should be based on a thorough assessment of the risks and benefits

Patients who receive CCI should be monitored for signs and symptoms related to coagulation activation or thrombosis. Events that may occur include myocardial infarction, ischemic cerebrovascular accident, arterial thrombosis (e.g. aorta, intestinal), deep venous thrombosis (DVT), and pulmonary embolism (PE). In case the patient displays signs and symptoms of any of these arterial/venous thrombotic events during the study, the physician in charge will assess the symptoms, order, and review diagnostic procedures (electrocardiogram (ECG), ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), Doppler, D-dimer, etc) as appropriate to confirm or refute the diagnosis. In case of symptoms suggestive of a DVT or PE, the guidelines for diagnosis as published by the American College of Physicians (Qaseem et al., 2007[28]) are suggested as guidance for determining the need for additional diagnostic tools.

Moreover, in case laboratory tests confirm either intravascular coagulation or thrombosis, depending on the patient's condition, CCI dosing should be reduced, or treatment should be discontinued. CCI dose adjustment may be required based on known patient's responsiveness to FVIIa-containing bypassing agents during prior bleeding events.

To note, a risk of thromboembolic events has been reported with the combination of bypassing agents and emicizumab (Oldenburg, 2017). This risk has been identified mostly with aPCC and (to a smaller extent) with rFVIIIa; specific emphasis will be put on the observation of the patient directly after administration of CCI as well as during the follow-up assessments to detect the occurrence of any thromboembolic events. Due to the heightened risk of thrombotic events and/or thrombotic microangiopathy with aPCC use in patients on emicizumab, aPCC will be allowed as rescue therapy at a total daily dose <100 U/kg (a single dose of aPCC should not exceed 50 U/kg) with discontinuation of TXA (Gundabolu et al., 2020[29]; Knoebl et al., 2021[30]).

If CCI treatment does not result in adequate hemostasis, development of neutralizing antibody should be suspected, and testing should be performed as clinically indicated.

4. OBJECTIVES AND ENDPOINTS

4.1. Objectives

4.1.1. Primary objective

The primary objective of this study is 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.

4.1.2. Secondary objective

The secondary objective of this study is to assess the safety of CCI

4.2. Endpoints

4.2.1. Primary efficacy endpoint

The primary efficacy endpoint is the proportion of successfully treated major procedures defined by a good or excellent global hemostatic response.

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 Section 9.2) 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).

The global hemostatic response will be considered:

- Excellent if the aggregate score from the 3 timepoints is between 7 and 9 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 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 with no score <1 for any of the component score comprising the aggregate score or between 5 and 6 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 when including at least 1 score = 0 or missing (without a replacement score) for any of the component score comprising the aggregate score (see Table 13–1).

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 or, at 24 or 120 hours after surgical wound closure is missing, then 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.

4.2.2. Secondary endpoints

- 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: 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) (see Table 9–1)
- 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 (see Table 9–1)
- 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: at 24 hours post-surgical wound closure (based on data collected during the 24-hour PO period, i.e. 0-24 hours period) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours)
- 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 period) and 120 hours post-surgical wound closure (based on data collected during the 120-hour PO period, i.e. 0-120 hours)
- Mean change in Hb level from initiation of the surgery until last visit
- 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)
- Mean number of bleeding episodes at the surgical site between surgical wound closure and last visit
- Mean number of surgical interventions/re-explorations for bleeding episodes between surgical wound closure and last visit
- Number of deaths from bleeding attributed to ineffective hemostasis
- Number and incidence of TEAEs (i.e. all AEs that occur at the time of or after the IMP administration until follow-up phone call) and 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 (fibrinogen and D-dimer levels)

4.2.3. Exploratory endpoint

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

4.2.4. Justification of endpoints

Justification of the primary endpoint

- The use of the 4 point-scale for hemostasis efficacy assessment is recommended by the WFH and used in all clinical studies (see Section 9.2.1). Minor adjustments to the blood loss criteria were made from the WFH scale (e.g. "not more than 10% greater" adjusted to "not more than 20% greater" to be assessed as Excellent) to reflect the expected differences in the specific inhibitor study population as compared to the overall hemophilia population considered for the published scale.
- The time period of 5 days, i.e. 120 hours post-operative, is justified by:
  - It has been recommended by hemophilia experts (hematologist and surgeon) based on the argument that majority of bleeds complications will occur in the first 72 hours and could still occur in some surgeries (e.g. total knee replacement) during the next 2 days.
  - Expecting that most of the major procedures to be evaluated in the study should be orthopedic surgeries, physical therapy will be required for most of the patients. The protocol specifies that physical therapy may not be initiated until 96 hours after wound closure, thus completing the evaluation at 120 hours post-surgical wound closure ensures that there is limited variability in the initiation of physical therapy. Beyond Day 5, specific regimens and durations of physical therapy are expected to be highly variable between patients.
  - Day 5 has been used in clinical studies for peri-operative efficacy assessment (e.g. Shapiro, 1998[8]).
  - The definition of the 120-hour PO period, which includes the 0-24 hours period, increases the weight of the 0-24 hours PO period, considered as a period of greatest trauma and thus of greatest bleeding risk.
  - The exclusion of score <2 for any of the component score in the definition of an "excellent" response and of IO and 120-hour PO scores <2 and 24-hour PO score <1 in the definition of a "good" response also increase the weight of the hemostasis response during the periods of greatest trauma and of greatest bleeding risk and reduce the impact of a declining hemostatic efficacy trajectory over time in the definition of success.

Justification of the other endpoints (Table 4–1)

Most of endpoints from PERSEPT 3 were kept as they were considered to be relevant.

Table 4–1: Secondary endpoints and justifications

Secondary endpoints	Time frame of data recorded	Justification for endpoints
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale	IO period	Component of the global hemostatic score for the primary endpoint Previously used in PERSEPT 3

Secondary endpoints	Time frame of data recorded	Justification for endpoints
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale by timepoint	24-hour PO period 120-hour PO period	Component of the global hemostatic score for the primary endpoint
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale at each timepoint post 120 hours after surgical wound closure	From 120 hours post-surgical wound closure to D15 or hospital discharge if earlier	Extended view of efficacy of CCI from the primary assessment time period. Expected to be correlated with primary endpoint, completing the peri-operative period across all patients/procedures.
Mean difference between actual measurable blood loss and maximum predicted blood loss in a similar patient without a bleeding disorder for the same major procedure as determined	IO period	Component of the global hemostatic score for the primary endpoint
Mean difference between actual measurable 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	24-hour PO period 120-hour PO period	Component of the global hemostatic score for the primary endpoint
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 Type: transfusion of blood, red blood cells, platelets, and other blood products Hb will be recorded at each transfusion need	IO period 24-hour PO period 120-hour PO period	Component of the global hemostatic score for the primary endpoint
Mean change in Hb level	From start of the surgery until last visit	Previously used in PERSEPT 3
Mean amount of CCI used to maintain hemostasis	From initial loading dose to last IO dose From initial loading dose through 120 hours post-surgical wound closure From initial loading dose through discharge From discharge through last dose For specific reasons (e.g. physical therapy, or other reasons like tourniquet, drain or suture removal)	Total dose through full 5 days common peri-operative period through discharge accounts for variable inpatient stay and flexibility in dosing interval Discharge through last visit accounts for variable outpatient dosing duration and dosing intervals Previously used in PERSEPT 3
Mean number of bleeding episodes at the surgical site and mean number of surgical interventions/re-explorations for bleeding episodes Any clinically relevant bleeding episodes	From surgical wound closure until last visit	Previously used in PERSEPT 3
Number of deaths from bleeding attributed to ineffective hemostasis	From start of the surgery to last phone call	

Secondary endpoints	Time frame of data recorded	Justification for endpoints
Number and incidence of TEAEs and AESIs	From first dose of CCI until last phone call	Previously used in PERSEPT 3
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)	At screening, within 24 hours prior to surgery and, at 24±4 hours after surgical wound closure, every 7±1 days from discharge to last dose of CCI for peri-operative management included (for hematology parameters) and at last visit	Previously used in PERSEPT 3
Mean value at each timepoint and mean change from baseline to each post-baseline timepoint in vital signs	At screening, within 24 hours prior to surgery, every 24±4 hours after surgical wound closure until hospital discharge, every 7±1 days from discharge to last dose of CCI for peri-operative management included and at last visit	Previously used in PERSEPT 3
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	At screening, within 24 hours prior to surgery, every 7±1 days from hospital discharge to last CCI dose for peri-operative management, at last CCI dose for peri-operative management, and at last visit	Previously used in PERSEPT 3
Mean value at each visit and mean change from baseline to each visit in coagulation-related parameters (fibrinogen and D-dimer levels)	At screening, just prior to surgery, immediately after surgical wound closure [T0 (i.e. wound closure) and T8 hours], and every 24±4 hours post-surgical wound closure until hospital discharge	Close follow-up of the hypothetical risk of thrombo-embolic events with the association of bypassing agents and emicizumab

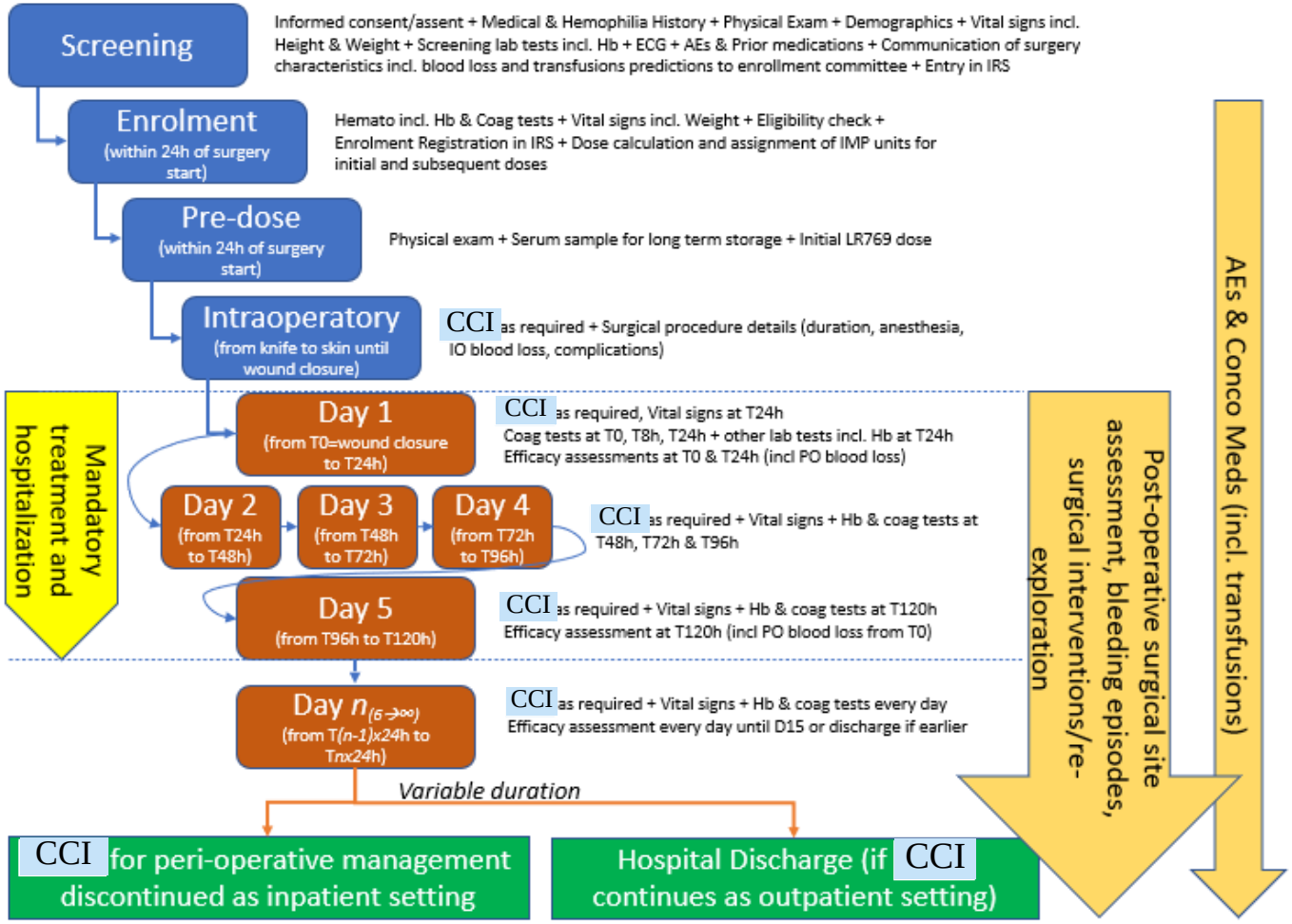
5. STUDY DESIGN

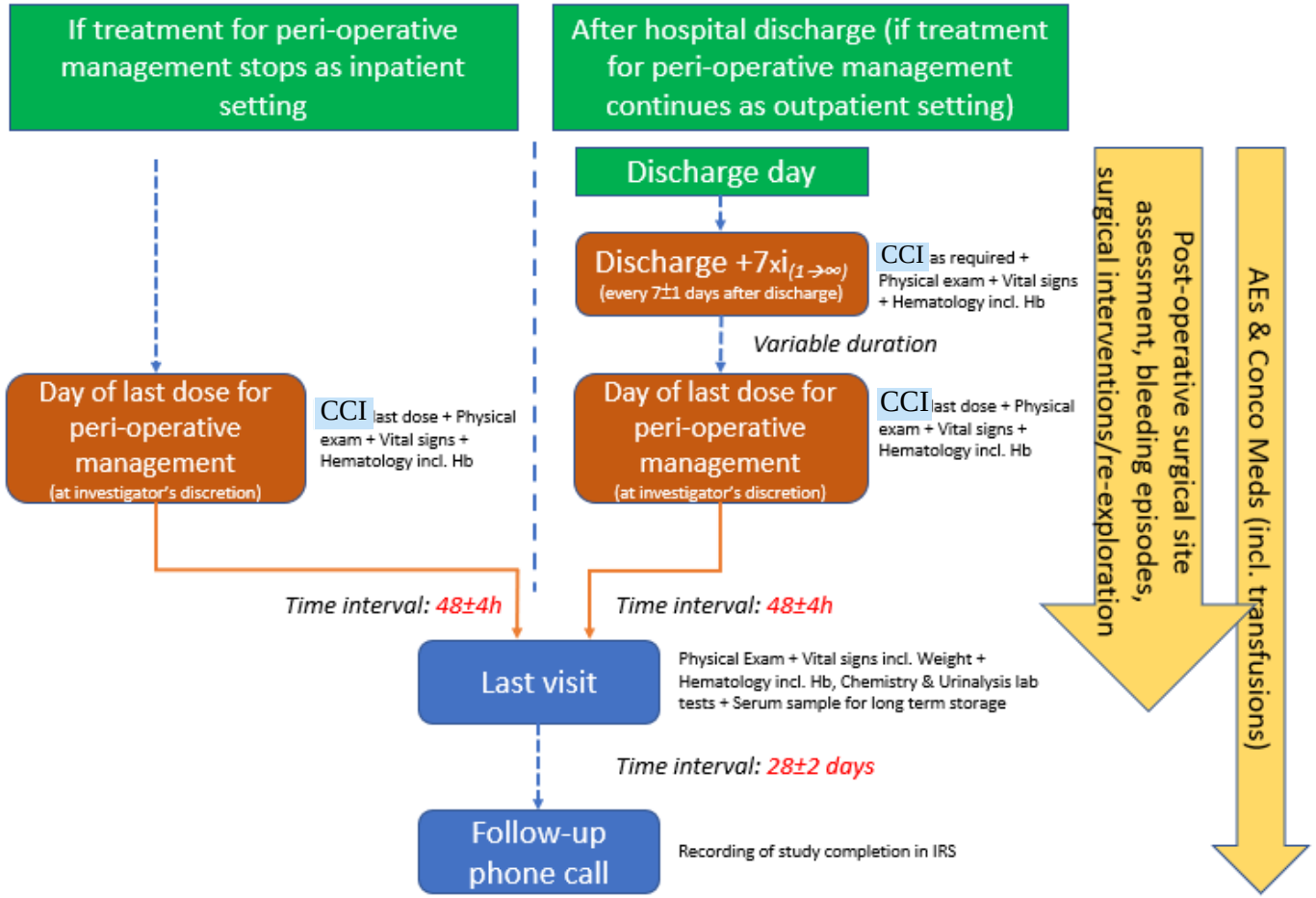
5.1. Overall Design

This is an international, multicenter, single-arm, Phase 3, and sequential study. An interim analysis will be conducted after 13 patients have been enrolled into the study and their primary efficacy endpoint evaluability determined. This interim analysis will be performed under the supervision of a DMC assigned to monitor the study (see Section 10.4.6). This will allow early termination of the study for efficacy or futility or the continuation of the study till completion. During the interim analysis, the screening and the enrolment of patients will be sustained. 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.

The visit diagram and procedures are presented in Figure 5–1.

Figure 5–1: Visit diagram and procedures





Abbreviations: AEs, adverse events; coag, coagulation; conco meds, concomitant medications; ECG, electrocardiogram; Hb, hemoglobin; inclu., including; IMP, investigational medicinal product; Inv, investigator; IO, intra-operative; IRS, interactive response system; PO, post-operative;

After obtaining informed consent (/child assent for minors) from the patient and/or the patient's parent(s)/legal guardian(s), patients who are scheduled for an elective major surgical procedure will undergo screening assessments to determine eligibility. During the screening period, the pre-enrolment predictions will be made by the surgeon/investigator and approved by an enrolment committee (see Section 9.1.1. 3). Patients who meet all eligibility criteria must be registered within 24 hours prior to surgery in an interactive response system (IRS) by the site staff to be considered as enrolled.

Treatment: Prior to surgery, the patient will receive intravenously the first CCI dose. The initial CCI dose will be followed by subsequent CCI doses to manage bleeding associated to surgery according to the investigator's judgment and the dosing guidelines specified in Table 7–2. The patient will be treated in hospital for at least 5 days. If the patient needs further treatment with CCI after hospital discharge, the patient will self-administer CCI at home.

Efficacy assessments*:* Immediately after surgical wound closure, the patient's IO response to treatment with CCI will be assessed by the surgeon and recorded as "excellent," "good," "moderate," or "poor" based on a 4-point scale. These responses will be assigned scores of 3, 2, 1 or 0, respectively. Subsequent efficacy assessments will be carried on by the investigator or designee at 24±4 hours and 120±4 hours post-surgical wound closure with scores also assigned at those timepoints. Then, the efficacy will be assessed every 24±4 hours until D15 or hospital discharge if earlier using the same 4-point scale. The observed responses will be recorded as "excellent," "good," "moderate," or "poor", but no score will be assigned any more. For details on the 4-point scale, please see Section 9.2.1.

***Safety assessment*:** Patients will be assessed for safety throughout the study until the follow-up phone call via physical examinations, assessments for signs and symptoms of thromboembolic events and hypersensitivity reactions, PO surgical site assessments, clinical safety laboratory tests, vital signs, and the recording of AEs and concomitant medications including transfusions if any. For details, please see Section 9.3. AESIs, SAEs and TEAEs will be followed by phone or other means until the date of follow-up phone call by the investigator or designee planned 28 ± 2 days after the last visit; all relevant details of these events will be recorded in the patient's source documentation and in the electronic case report form (eCRF).

The schedule of activities is presented in Table 1–1.

5.2. Scientific Rationale for Study Design

There are currently no European Medicines Agency (EMA) or Food and Drug Administration (FDA) guidelines for the development of FVIIa products. However, in Europe, there are guidelines for the development of FVIII and FIX products, including the most recently released guideline for the development of FIX products (EMEA/CHMP/BPWP/144552/2009 rev 1, Corr.1[31]). This guideline, currently under revision, has been updated to include pediatric studies in conformance with the pediatric regulations. In view of this, a stepwise approach following the basic principles of the FIX guideline has been adopted for the purposes of clinical development plan of CCI

This is a single-arm, sequential, non-comparative study as a control arm is not feasible. A placebo cannot be used, as that would result in insufficient prevention of bleeding associated with the procedure, leading to potentially irreversible damage to the patient, or could even be life threatening. A comparison with current standard of care would then be the next best option, which in this case could either be aPCC (FEIBA®) or FVIIa concentrate (i.e. NovoSeven® RT). Such studies would need

to be designed as a non-inferiority study, and the most obvious comparator would be NovoSeven® RT as it is most used in the developed world for this indication. However, if powered sufficiently, the size of such a study would not be feasible. Therefore, the sample size was selected based on FIX guidance in agreement with US and EU health authorities.

5.3. Justification for IMP Dose

The CCI treatment regimen used in this study is selected based on a Phase 1b study assessing the PK and pharmacodynamic (PD) effects of 3 doses of CCI (25, 75, 225 µg/kg) in hemophilia A or B patients, as well as from a Phase 3 study (PERSEPT 1) which confirmed the clinical efficacy of 75 and 225 µg/kg CCI initial dose regimens for the treatment of bleeding episodes. Based upon the demonstrated PK/PD relationship, to account for the extensive tissue damage in major surgical procedures and resulting greater hemostatic challenge, a dose of 200 µg/kg (previously used in PERSEPT 3 [Escobar et al., 2021[32]) before a major surgical procedure will be used. These doses are expected to provide a clinical effect that will be sufficient to effectively prevent excessive bleeding during and after surgical/invasive procedures and achieve and maintain hemostasis. Additional doses of 75 µg/kg for the post-procedure setting are outlined in detail in Section 7.1.1. 2.

Efficacy and safety results of the Phase 3 study (PERSEPT 1) in patients 12 years and older provide evidence that on-demand CCI doses of 75 µg/kg every 2 or 3 hours effectively control bleeding episodes in hemophilia A or B patients with inhibitors. The results of this study and of the Phase 1b are more extensively described in the current CCI IB.

5.4. End of Study Definition

The end of the study is defined as the follow-up phone call performed by investigator or designee to the last patient in the study, 28 ± 2 days after the last visit.

A patient is considered to have completed the study if he has completed all visits of the study including the last visit and received the phone call 28 ± 2 days after the last visit from investigator or designee as shown in Table 1–1.

6. STUDY POPULATION

The population for this study is male patients, aged 12 years to 65 years, inclusive, who have congenital hemophilia A or B complicated by current high titer inhibitors (peak BU ≥5), or history of high responding inhibitors (BU ≥5) or expected to have a strong memory (anamnestic) response after re-exposure or to be refractory or intolerant to FVIII or FIX concentrates usage and who are scheduled for an elective major surgical procedure. Since patients with an anamnestic response and those refractory or intolerant to factor concentrates cannot be treated with these products, they represent candidates for inclusion in this study.

Patients who were participating in previous CCI study will be allowed in this study.

Only elective major surgical procedures will be allowed in the study.

6.1. Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. be male with a diagnosis of congenital hemophilia A or B of any severity

2. have one of the following:

   a. current positive inhibitor test BU ≥5 (as confirmed at screening by the institutional lab) or history of high-responding inhibitors (BU ≥5) not further successfully treated by Immune Tolerance Induction

   OR

   b. a condition precluding the use of FVIII or FIX products to treat or prevent bleeding such as a previous anamnestic response after exposure to factor concentrates or a previous failure to respond to FVIII or FIX concentrates

3. be ≥12 years to ≤65 years of age on the day of informed consent

4. be scheduled for an elective major surgical procedure as defined in the study protocol (see Table ''Definitions for the specific purpose of Study F7TG2202'')

5. have Hb ≥12 g/dL (WHO/NMH/NHD/MNM/11.1[33])

6. be capable of understanding and willing to comply with the conditions of the protocol OR in the case of a patient under the age of legal majority, parent(s)/legal guardian(s) must be capable of understanding and willing to comply with the conditions of the protocol

7. have read, understood, and provided written informed consent (patient or parent(s)/legal guardian(s) if the patient is minor according to local regulation) and, where applicable according to local regulation, patient's assent if the patient is minor

6.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. have any coagulation disorder other than hemophilia A or B

2. be immunosuppressed (i.e. the patient should not be receiving systemic immunosuppressive medication; CD4+ cell counts at screening should be 200/µL)

3. known intolerance to CCI or any of its excipients

4. currently receiving immune tolerance induction (ITI) therapy

5. have a known or suspected allergy or hypersensitivity to rabbits or rabbit proteins

6. have platelet count <100,000/µL

7. have received an investigational drug within 30 days or within 5 half-lives of that investigational drug, whichever is longer, of the planned first CCI administration, or be expected to receive such drug during participation in this study. Patients who have received fitusiran in a clinical study may not participate in this clinical study for 6 months since the last dose and if they have an antithrombin III level not in the normal range at screening.

8. for patients using emicizumab, have received during the last 6 months or currently receiving a maintenance dosing regimen of emicizumab different from the indicated one (± 10% of approved dose), i.e. different from 1.5 mg/kg once weekly (± 10%), 3 mg/kg (± 10%) every two weeks or 6 mg/kg (± 10%) every four weeks

9. for patients using emicizumab, currently be any plans, or notes in the patient's medical records that would suggest the need to increase or decrease emicizumab dosing due to antidrug antibodies (ADAs), reduced PK, or coagulation/safety-related issues (e.g. lack of response, or potential/actual thromboembolic concerns, etc)

10. have a clinically relevant hepatic (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] >3 times the upper limit of normal [ULN]) and/or renal impairment (creatinine >2 times the ULN)

11. have a history of arterial and/or venous thromboembolic events (such as myocardial infarction, ischemic strokes, transient ischemic attacks, DVT, or PE) within 2 years prior to the planned first dose of CCI uncontrolled arrhythmia, or current New York Heart Association (NYHA) functional classification score of stages II – IV

12. have an active malignancy (those with non-melanoma skin cancer are allowed)

13. have any life-threatening disease or other disease or condition which, according to the investigator's judgment, could imply a potential hazard to the patient, or interfere with the study participation or study outcome (e.g. chronic, unmanaged hepatitis infection)

14. be using aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), herbs, natural medications, or other drugs with platelet inhibitory properties within one week prior to surgery and for the duration of treatment with CCI

15. have active gastric or duodenal ulcer disease

16. have received a FVII- or FVIIa-containing product (either plasma derived or recombinant) within 24 hours prior to administration of CCI

17. have a contraindication to antifibrinolytics

18. have planned combined major surgeries at the same time or have already been enrolled and treated for a previous elective major surgery in the same SCOPE HIM study

19. be administered pharmacologic thromboprophylaxis within 5 half-lives of that medication before surgery or for the duration of treatment with CCI

6.3. Lifestyle Considerations

Not applicable.

6.4. Screen Failures

In case of screen failure, re-screening will be allowed when the criteria leading to non-eligibility are temporary.

Re-screened participants will sign a new informed consent/child assent, be assigned with a new patient number, and repeat all screening tests.

Regardless of whether a participant is screen failed or enrolled, an eCRF will be completed for each patient who signs a consent form or for whom the consent form is signed by the patient's parent(s) or legal representative(s) and who has given where applicable under local regulations his assent. In case of screen failure, the reason will be documented in the patient's medical file.

6.5. Strategies for Recruitment and Retention

Patients who are removed from the study will only be replaced if their removal prevents to reach a minimum of 17 evaluable patients for the primary efficacy endpoint.

Patients who would not fully comply with the consenting process as per local regulation (e.g. incomplete consent form, missing assent where required, missing legal representative's signature where applicable, etc.) will be removed from the study and replaced.

7. STUDY MEDICATION

7.1. Investigational Medicinal Product (IMP)

The CCI IB in force is the reference document of the IMP.

7.1.1. IMP administration

7.1.1. 1. IMP description

The IMP for this study will be a FVIIa product called CCI It is produced using recombinant technology. The purification process can remove host-related impurities and/or any potential viruses.

CCI will be available as a lyophilized powder in single-use vials containing 5 mg of coagulation FVIIa (recombinant)-jncw (Anatomical Therapeutic Chemical [ATC] code: B02BD08). After reconstitution with the appropriate volume of sterile water for injection (WFI) provided in a prefilled syringe, each milliliter contains 1 mg (1000 µg) of CCI

The IMP will be provided by the sponsor.

The qualitative and quantitative composition of CCI is shown in Table 7–1.

Table 7–1: Qualitative and quantitative composition of CCI 5 mg vial

Components	Amount per 5 mg vial
Coagulation Factor VIIa (Recombinant)	5 mg
Arginine HCl (USP/Ph. Eur.)	CCI
Isoleucine (USP/Ph. Eur.)	CCI
Trisodium Citrate Dihydrate (USP/Ph. Eur.)	CCI
Glycine (USP/Ph. Eur.)	CCI
Lysine HCl (USP/Ph. Eur.)	CCI
Polysorbate 80 (USP/Ph. Eur.)	CCI

Ph. Eur. = European Pharmacopoeia; USP = United States Pharmacopeia

Further information can be found in the CCI IB.

7.1.1. 2. Dosing and administration

Inpatient dosing:

- Initial treatment: An IV dose of 200 µg/kg of CCI infused within ≤2 minutes will be used as the initial dose before the start of the surgery.
- Follow-up treatment: The initial dose of CCI (200 µg/kg) will be followed for the IO period and the first 72 hours post-surgical wound closure by repeated administration of IV bolus doses of 75 µg/kg of CCI infused within ≤2 minutes every 2 hours ±15 minutes. Then, the dose frequency of administrations will be adjusted according to Table 7–2. The minimum duration of CCI treatment will be 5 days at hospital.

Outpatient dosing: If the patient needs further treatment with CCI after hospital discharge, the patient will self-administer CCI at home according to the investigator's judgment and the dosing guidelines specified in Table 7–2. The patient will be provided with CCI administration kits, associated materials and directions for its storage, reconstitution, and administration along with a patient's diary to record CCI administrations.

Table 7–2: Doses and dosing schedules of CCI for major surgical procedures

Inpatient dosing		
Day	**Dose**	**Interval**
Immediately prior to surgical incision	200 µg/kg	Initial dose (within 2 minutes prior to surgical incision)
Intra-operative period	75 µg/kg	Every 2 hours (± 15 minutes)
Day 1 (wound closure) through Day 3 (72 hours from wound closure)	75 µg/kg	Every 2 hours (± 15 minutes)
Day 4 (post 72-hour assessment)	75 µg/kg	Every 2 hours (± 15 minutes) to 4 hours (± 15 minutes)
Days 5-6*	75 µg/kg	Every 2 hours (± 15 minutes) to 6 hours (± 15 minutes)
Days 7+*	75 µg/kg	Every 2 hours (± 15 minutes) to 8 hours (± 15 minutes)
Outpatient dosing		
Day	**Dose**	**Interval**
From hospital discharge to last dose for peri-operative management**	75 µg/kg	Every 2 hours (± 15 minutes) to 12 hours (± 15 minutes)

**Dosing beyond D5 will be optional*

***Hospital discharge will be at the judgment of the investigator but will not occur until i) after the 120-hour efficacy assessment AND ii) the patient is successfully maintained at every 6 hours or greater dosing interval. Dosing frequency may be increased only with the investigator recommendation in the outpatient setting as needed.*

NOTE: If clinically indicated because of oozing or similar findings suggesting the need for more frequent CCI infusions, the treatment interval may be shortened in consecutive doses within the margins stated in Table 7–2.

If physical therapy is planned, an IV bolus dose of 75 µg/kg of CCI infused within ≤2 minutes is mandated each time before physical therapy begins. Note that patients should not undergo physical therapy before 96 hours post-surgical wound closure (with no great range of motion, gradually). This bolus dose will not be considered as an IMP extradose. After D15 post-surgical wound closure, the switch from CCI to conventional therapy will be allowed and expected from the moment CCI becomes no longer required for peri-operative management but only used as a bleeding prevention treatment associated to physical therapy.

Similarly, before tourniquet, drain or suture removal, an IV bolus dose of 75 µg/kg of CCI infused within ≤2 minutes is recommended. This bolus dose will not be considered as an IMP extradose.

7.1.2. Preparation/Handling/Storage/Accountability

The supply manual describes the appropriate procedures about receipt, storage, preparation, handling, return, and destruction of the IMP.

7.1.2. 1. Acquisition and accountability

Shipment and IMP reception

Shipments of IMP to hospital pharmacy or investigational service will be organized by the CMO at a controlled temperature, either refrigerated between +36°F and +46.4°F (between +2°C and +8°C) or ambient between +59°F and +77°F (between +15°C and +25°C).

Upon receipt, the pharmacist or designee will verify the condition, content, and quantity of IMPs. He/she will complete the acknowledgement of receipt form and send it gathered with the temperature extraction to the CMO and/or sponsor. Should any abnormality of the supply boxes be observed, the pharmacist or designee must immediately inform the drug distributor and the sponsor.

Re-supply of IMPs to the site will be organized as necessary by the CMO upon request.

IMP dispensing

The investigator is responsible for dispensing the IMP through the IRS, on several occurrences dependent on the dosing schedule and the evolution of the patient's hemostasis. If a patient needs to self-administer the IMP at home after hospital discharge, the investigator should dispense to the patient a quantity of IMP that is sufficient to cover the patient's needs until next scheduled visit, calculated according to the prescribed dosing frequency. The investigator is allowed in that case to dispense an additional amount that could cover the patient's needs for up to additional 48 hours beyond the next scheduled visit in case the patient is forced to postpone his scheduled visit for any reason. Dispensing CCI may be delegated (e.g. to a hospital pharmacy) as locally applicable.

IMP accountability

The investigator is responsible of the IMP accountability at site. Patients who are given CCI for home administration will be instructed to return the used and any unused vials to the site and to document their CCI administrations on their diary. The study specific accountability forms should be filled, monitored, reconciled with the diaries, and provided to the sponsor. All explanations for non-compliance must be documented. The accountability should be up to date at any time. This documentation must be available for review by the monitor at the monitoring visit to confirm proper CCI management.

Return and destruction

The return preparation of used/unused IMPs including those returned by patients who self-administered CCI at home will be performed by the pharmacist and the monitor.

The used, partially used, and unused vials will be handled according to the local regulations and according to the instructions provided by the sponsor.

The pharmacist or designee must not destroy the used/unused IMP vials without written authorization from the sponsor. In case of destruction on site required by local regulation, a destruction certificate, as well as the site destruction procedure, should be provided to the sponsor.

At the end of the study, accountability records will be reconciled with delivery records, dispensing records and destruction certificates (if applicable).

7.1.2. 2. Formulation, appearance, packaging, and labeling

Formulation

See Section 7.1.1. 1.

Packaging

CCI will be supplied in clear glass vials as lyophilized powder (5 mg). Vials will be packed in secondary packaging including prefilled syringes, as well as supplies for reconstitution of CCI

Each vial of CCI will be packed in a secondary packaging, i.e. sealed cardboard box labeled according to the study.

Labeling

Secondary packaging, glass vials, and prefilled syringes with sterile WFI for reconstitution will be labeled using multilingual labels that will comply with Good Manufacturing Practice, Annex 13, and with local regulations and requirements.

7.1.2. 3. Product storage and stability

CCI must be stored in a safe and secure place at the study site or at home. CCI will be stored between +36°F to +86°F (+2°C to +30°C), protected from light in the product package, and must not be frozen. After reconstitution, CCI should be stored at room temperature, but can be stored between +36°F to +86°F (+2°C to +30°C), for up to 4 hours. CCI must not be frozen or stored in syringes.

The investigator is fully responsible for CCI stored at the study site. Access at the study site will be strictly limited to the investigator and designated staff. Neither the investigator nor designated staff may provide CCI to any subject not enrolled in the study.

7.1.2. 4. Preparation

Using the appropriate size vial adapter (supplied), reconstitute each 5 mg vial with the supplied 5.2 mL prefilled syringe to obtain a final concentration of 1 mg/mL CCI Slow WFI injection and gentle swirl of the vial should be done to prevent foaming while reconstituting.

It is recommended that the product only be reconstituted just prior to administration and used within 4 hours of reconstitution, since CCI does not contain preservatives. Use only the preparation and administration supplies provided by LFB.

Detailed instructions for preparation and administration of IMP will be described in the Instruction for Use (IFU).

7.1.3. IMP compliance

All patients will be treated with CCI in the hospital prior to, during, and immediately after the surgical procedure for at least 5 days. Patients may be discharged from the hospital and treated at home at the investigator's discretion. During the patient's hospitalization for the procedure, compliance is managed by the site staff who will record the date, the exact dose, start and stop times of infusion. If the patient continues treatment with CCI after discharge from the hospital, he will be given a patient's diary in which record the date, the exact dose, start and stop times of CCI administrations as well as the number of vials used. These data will be checked by the study staff at the next visit to the study site and compared to the number of vials returned and those remaining at the patient's home.

Interruption or premature termination of CCI infusion should be documented in the patient's medical file and the eCRF.

Reasons for any non-compliance must be recorded in the patient's diary and/or medical file.

7.2. Study Material

The sponsor will supply study material (administration kits, waste containers…) free of charge to the sites and at home administration. For further details, please refer to the supply manual.

7.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable as this is an open-label study.

7.4. Concomitant Therapy

7.4.1. Prior medication

Medications that start and stop prior to the date of IMP infusion will be classified as "prior" medications.

All relevant prior medications to the patient's cardiac condition taken within one month prior to the IMP administration must be recorded in the patient's medical file and the eCRF. Moreover, any prior medication taken more than one month prior to the IMP administration which is, in the opinion of the investigator, clinically relevant to the patient's condition will also be recorded.

All procedure agents (i.e. medication given for the surgery) must be recorded in the patient's medical file and the eCRF.

The prior medications prohibited during the study are detailed in Section 7.4.3.

7.4.2. Concomitant medication

A medication that starts on or after the date of first IMP infusion or starts before and is ongoing on the date of first CCI infusion will be classified as "concomitant" medication.

The concomitant medications forbidden during the study are detailed in Section 7.4.3.

Other medications which were necessary for the patient's welfare or well-being may be given at the investigator's discretion.

Any concomitant medications must be recorded in the patient's medical file and the eCRF.

7.4.3. Forbidden medication

The following medications are forbidden:

- Current use of ITI therapy
- Administration of an investigational drug within 30 days or within 5 half-lives of that investigational drug, whichever is longer, of the planned first CCI administration, or during the study. Patients who have received fitusiran in a clinical study may not participate in this clinical study for 6 months since the last dose and if they have an AT III level not in the normal range at screening.
- For patients using emicizumab:
  - A maintenance dosing regimen of emicizumab different from the indicated one (± 10% of approved dose), i.e. different from 1.5 mg/kg once weekly (± 10%), 3 mg/kg (± 10%) every 2 weeks or 6 mg/kg (± 10%) every four weeks during the last 6 months or currently
  - Need to increase or decrease emicizumab dosing due to ADAs, reduced PK, or coagulation/safety-related issues (e.g. lack of response, or potential/actual thromboembolic concerns, etc.) during the study
- Aspirin, NSAIDS, herbs, natural medications, or other drugs with platelet inhibitory properties within one week prior to surgery and for the duration of treatment with CCI
- A FVII- or FVIIa-containing product (either plasma derived or recombinant) within 24 hours prior to administration of CCI
- Pharmacologic thromboprophylaxis within 5 half-lives of that medication before surgery or for the duration of treatment with CCI (only thromboprophylaxis mechanical will be allowed and encouragement of frequent calf pump exercises)

7.5. Rescue Medication

The rescue therapy will be given in case the response to CCI is considered insufficient (i.e. treatment failure), based on the investigator's judgment.

The rescue therapy will include (Jimenez-Yuste, Auerswald et al., 2021[34]; Jimenez-Yuste, Rodriguez-Merchan et al., 2021[23]; Escuriola-Ettingshausen et al., 2021[35]):

- Other rFVII: Novoseven at the dose of 90 µg/kg every 2 hours: in case of excessive bleeding, increase the dose (up to 270 µg/kg) or shorten the interval between doses until bleeding is controlled with a cumulative dosing consistent with the approved labelling
- For patients with low-inhibitor titer (<5 BU), human FVIII concentrates; it should be given under control of FVIII:C and regular inhibitor testing.
- Porcine FVIII as a potential alternative for a high-titer patient and when bleed control cannot be achieved with human FVIII
- aPCC as the last alternative at a total daily dose <100 U/kg (a single dose of aPCC should not exceed 50 U/kg) until bleeding is controlled with the relevant laboratory parameters closely monitored for thromboembolic events, thrombotic microangiopathy and with discontinuation of TXA, if administered, for patients on emicizumab
- TXA as rescue therapy i.e. if prophylactic administration not planned prior to surgery

The date and time of rescue therapy administration as well as the name and dosage regimen of the rescue therapy must be recorded in the patient's medical file and the eCRF.

8. IMP DISCONTINUATION AND PARTICIPANT DISCONTINUATION / WITHDRAWAL

8.1. Discontinuation of IMP

IMP administration could be discontinued when an AE suspected to be related to the IMP occurs (e.g. thromboembolic events, allergic or anaphylactic-type reaction). Patient's treatment should be modified according to the local medical practice. The date and reason for discontinuation of IMP should be accurately documented in patient's source documentation and the eCRF, as well as the planned new treatment to be administered if any.

8.2. Participant Discontinuation/Withdrawal from the Study

The patient is free to withdraw from participation in this study at any time, for any reason, and without prejudice. The investigator must withdraw any patient who requests to stop participating in the study. Patient who withdraws his consent will be asked to undergo the assessments scheduled at the last visit. He will be advised that participation to the last visit is voluntary but is in his best interest.

The investigator or the sponsor may withdraw a patient from the study for any of the following reasons:

- Occurrence of an AE related to IMP that justifies the discontinuation of the IMP
- Protocol deviation that could endanger the patient safety or invalidate the interpretation of the study
- If the patient meets an exclusion criterion (either newly developed or not previously recognized)

In case of withdrawal, the investigator will make every effort to perform the assessments scheduled at the last visit. All results, the date of the end of study and the reason(s) for withdrawal must be recorded in the source documents and the eCRF.

If the reason of withdrawal is an AE, the investigator will seek to obtain follow-up information and to document the event until its resolution or stabilization.

8.3. Lost to Follow-up

A patient will be considered as lost to follow-up only after the investigators have made every effort to contact the patient and/or his family or relatives to obtain the maximum of the per protocol (PP) requested information. All contact attempts will be documented in the patient's medical files. Patients lost to follow-up will be considered as withdrawn from the study.

9. STUDY PROCEDURES AND ASSESSMENTS

9.1. Study Procedures

9.1.1. Screening period

9.1.1. 1. Informed consent/assent process

9.1.1. 1.1. Consent/assent and other informational documents provided to participants

The investigator will provide each major patient and each minor patient's parent(s) or legal representative(s) with relevant, comprehensive, verbal, and written information regarding the nature and purpose of this study, its objectives and procedures, and the possible risks involved. The major patient or the minor patient's parent(s) or legal representative(s) will be notified that CCI will be done in the hospital for at least 5 days. The investigator will explain that, even if the patient/parent(s)/legal representative(s) allows the participation in the study and signs an informed consent form (ICF) (including if the minor patient signs a child assent form), the study specific tests or procedures at screening may demonstrate that the patient is not a candidate for the study.

The investigator, where applicable under local regulations, will also provide the minor patients with an age- and language-appropriate child assent form, which will describe the same relevant, comprehensive, written information about the study.

The patient/parent(s) or legal representative(s) should be given enough time to ask questions about the study, and to have their questions answered to their satisfaction by the investigator. The patient/parent(s) or legal representative(s) where applicable must be informed of the patient's right to withdraw from the study at any time, without prejudice regarding future treatment.

9.1.1. 1.2. Consent procedures and documentation

The major patient and one or both parent(s) or legal representative(s) of the minor patient, according to local regulations, will read and sign the ICF prior to having any study-related procedures performed on the patient. Minor patients, where applicable under local regulations, will read and sign the age- and language-appropriate child assent form prior to having any study-related procedures performed.

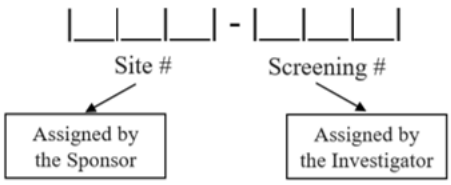
The original informed consent/assent forms, personally dated and signed by the patient and, where applicable, by the patient's parent(s) or legal representative(s), as well as by the investigator, will be filed in the investigator site file. The investigator will supply all patients and parent(s) or legal representative(s) of minor patients with a copy of their signed and dated informed consent/assent forms. Details of the informed consent/child assent discussions should be recorded in the patient's medical file.

If the informed consent/assent forms are revised, approval or favorable opinion of any revisions must be given by the independent ethics committee (IEC)/ institutional review board (IRB). It is the Investigator's responsibility to ensure that all patients subsequently entered the study and those currently in the study sign the amended ICF/assent form and all parent(s) or legal representative(s) of minor patients sign the amended ICF. These revised consent/assent forms will be documented in the same manner as previously described.

Patients who have completed the study and the parent(s) or legal representative(s) of minor patients should be informed of any new information that may affect the patients' welfare and safety.

9.1.1. 2. Patient allocation

The screened patients will be allocated a patient number composed of 6-digit numbers as shown below.



A three-digit number will be allocated to each site at the beginning of the study by the sponsor. Investigator will allocate a screening number to each screened patient. Screening numbers will be a three-digit number starting with 001 and attributed sequentially according to the chronological order of informed consent/assent form signature at the site.

9.1.1. 3. Screening visit (Days -28 to Day -1)

The following study procedures will be carried out:

- Informed consent/assent signature
- Check of eligibility criteria
- Demographic information (age, sex, ethnicity, and race). Note that the ethnicity and race will be collected to comply with FDA Guidance for Industry and Food and Drug Administration Staff, 2016[36].
- Disease characteristics / Hemophilia history
- Relevant surgical/medical history
- Collection of prior/concomitant medications
- Physical examination
- All laboratory tests (hematology including CD4+, coagulation including AT III only for patients with a history of treatment with fitusiran, serology, chemistry, urinalysis, inhibitor titer); For further details see Section 9.3.3.
- Predicted surgery characteristics by surgeon (and another investigator where required):

- Type of anesthesia
- Procedure description
- Prophylactic use of emicizumab or not, and dosing regimen if used
- Planned use of antifibrinolytics or not
- Expected maximum blood loss in mL for the same procedure for a similar patient (i.e. patient of the same sex, age, and stature) 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 hours 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
- Expected maximum number of units and volume (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 hours 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

These predicted surgery characteristics will be communicated to an enrollment committee comprised minimally of the expert surgeon competent in the surgery in patients with hemophilia and the sponsor's medical monitor, at least 3 working days before the date of the planned surgery, to allow discussions to take place, to mitigate the variability between centers and to consolidate the surgeon/investigator's predicted blood loss and blood component transfusion.

The enrollment committee must deliver their judgment within 48 hours upon receipt of information. In case of disagreement, a discussion must be set up to find a common ground. This can lead to a delay in the date of planned surgery if the agreement takes time. The final decision must be documented by the expert surgeon.

- Patient's screening registration in the set-up IRS, with documented date and time of informed consent
- Vital signs: Weight, height, systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- 12-lead ECG
- AEs assessment
- If applicable: Patient's screen failure entry in the set-up IRS, with documented date and reason of screen failure

9.1.2. Treatment period

9.1.2. 1. Prior to surgery

- Check of eligibility criteria within 24 hours prior to surgery
- Physical examination within 24 hours prior to surgery
- Patient's enrolment registration in set-up IRS within 24 hours prior to surgery after a mutual agreement between the site's surgeon (and another investigator where required), the expert surgeon from the enrollment committee and the sponsor's medical monitor on the adequacy of the candidate and on the blood loss and blood component transfusion predictions

- Vital signs within 24 hours prior to surgery:
  - Systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
  - Weight for calculation and assignment of IMP units for initial and subsequent doses
- Hematology tests: Complete blood count (CBC) including Hb, Hct, platelet count, red blood cell (RBC) count and white blood cell (WBC) count with differential
- Coagulation tests: Fibrinogen, D-dimer within 24 hours prior to surgery
- Collection of concomitant medications (including transfusion if any)
- AEs assessment
- Serum sample for long term storage before first CCI dose
- First CCI dose administration immediately prior to surgical incision
  - Collection of administered vials numbers and batch numbers
  - Collection of infusion parameters (administered doses, the date of administration and the start and end times). Interruption or premature termination of CCI infusion should be documented.

9.1.2. 2. During surgery

- Surgery characteristics
  - Duration
  - Actual measurable IO blood loss
  - Factors that may have influenced bleeding independent of hemostasis
  - Type of anesthesia
  - Complications if any
- CCI IO administration as required
  - Collection of administered vials numbers and batch numbers
  - Collection of infusion parameters (administered doses, the dates of administration and the start and end times). Interruption or premature termination of CCI infusion should be documented.
- Collection of concomitant medications (including transfusion if any)
- AEs assessment (including signs and symptoms for thromboembolic events and hypersensitivity reactions)

9.1.2. 3. From surgical wound closure to hospital discharge

In continuous throughout this period

- Collection of concomitant medications (including transfusion if any)
- Collection of number of bleeding episodes at the surgical site if any
- Collection of number of surgical interventions/re-explorations for bleeding if any
- AEs assessment (including signs and symptoms for thromboembolic events and hypersensitivity reactions)
- CCI administration as required
  - Collection of administered vials numbers and batch numbers
  - Collection of infusion parameters (administered doses, the dates of administration and the start and end times). Interruption or premature termination of CCI infusion should be documented.

Immediately post-surgical wound closure

- IO hemostatic efficacy assessment based on 4-point scale (Table 9–1)

- Coagulation tests: fibrinogen, D-dimer at T0 (i.e. wound closure) and T8h after wound closure

Every 24 ± 4 hours
- Post-operative surgical site assessment
- Hematology test: Hb
- Coagulation tests: Fibrinogen, D-dimer
- Vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

At 24 ± 4 hours post-surgical wound closure
- All chemistry tests
- All urinalysis tests
- Hematology tests: Hct, platelet count, RBC count, WBC count with differential

At 24 ± 4 hours and 120 ± 4 hours post-surgical wound closure, then every 24 ± 4 hours until D15 or hospital discharge if earlier
- Hemostatic efficacy assessment based on the 4-point scale (Table 9–1)

At hospital discharge
- Delivery of patient's diary with instruction for use. The patient should document in the diary any AE that occurs outside of hospital (including start and end date and time), CCI administration and any medication taken (including start and end date and time). The patient should come back at each visit with the diary and the investigator or designee should assess and evaluate patient information recorded in the diary and report appropriate relevant information in the eCRF.

9.1.2. 4. From hospital discharge to last CCI dose for peri-operative management

Every 7 ± 1 days
- Physical examination
- Vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- Hematology tests: Hb, Hct, platelet count, RBC count, WBC count with differential
- Post-operative surgical site assessment
- Collection of concomitant medications (including transfusion if any)
- Collection of number of bleeding episodes at the surgical site
- Collection of number of surgical interventions/re-explorations for bleeding if any
- AEs assessment (including signs and symptoms for thromboembolic events and hypersensitivity reactions)
- Patient's diary verification.

Every 2 ± 1 days
- Phone call to major patient or to minor patient's parent(s)/legal representative(s) to collect information about the possible occurrence of AEs after the patient has left the hospital, discuss dosing regimen, ask about physical therapy visits and remind for diary completion

9.1.2. 5. Day of last CCI dose for peri-operative management

- Physical examination
- Vital signs: systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- Hematology tests: Hb, Hct, platelet count, RBC count, WBC count with differential

- Post-operative surgical site assessment
- Collection of concomitant medications (including transfusion if any)
- Collection of number of bleeding episodes at the surgical site if any
- Collection of number of surgical interventions/re-explorations for bleeding if any
- AEs assessment (including signs and symptoms for thromboembolic events and hypersensitivity reactions)
- Patient's diary verification.

9.1.3. Follow-up period

9.1.3. 1. Last visit 48 ± 4 hours after last dose of CCI *for peri-operative management or in case of premature patient discontinuation*

- Physical examination
- Vital signs: Weight, systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.
- Hematology tests: Hb, Hct, platelet count, RBC count, WBC count with differential
- All chemistry tests
- All urinalysis tests
- Post-operative surgical site assessment
- Collection of concomitant medications (including transfusion if any)
- Collection of number of bleeding episodes at the surgical site if any
- Collection of number of surgical interventions/re-explorations for bleeding if any
- AEs assessment (including signs and symptoms for thromboembolic events and hypersensitivity reactions)
- Serum sample for long term storage
- Patient's diary verification and collection in the patient's medical file.

9.1.3. 2. Follow-up phone call 28 ± 2 days after last visit: end of study

A last follow-up phone call from the investigator or designee to the patient will be planned for:
- Collection of concomitant medications (including transfusion if any)
- AEs assessment (including signs and symptoms for thromboembolic events)
- Recording of patient's study completion in the set-up IRS

9.2. Efficacy Assessments

Every effort will be made to ensure that there are no missing assessments especially on critical data.

9.2.1. Hemostatic response: blood loss, blood component transfusion, IMP extradose

Hemostatic efficacy assessments will be performed according to existing guidelines and published literature (Shapiro et al., 1998[8]; Giangrande et al., 2009 [11]; Shapiro et al., 2012[37]; Shapiro, 2014[38]; Brand et al., 2016[39]; Gruppo et al., 2019[40]; Srivastava A et al., 2020[13]).

The hemostatic efficacy assessment will be based on 4-point hemostatic scale - "excellent", "good", moderate" and "poor" - for IO period, at 24 hours post-surgical wound closure, at 120 hours post-surgical wound closure and daily from 120 hours post-surgical wound closure to D15 or hospital

discharge if earlier according to the definition/criteria described in Table 9–1. Success will be defined for "excellent" and "good" ratings.

Table 9–1: 4-point scale for efficacy assessment during the intra-operative and the post-operative periods

Rating	Definition/Criteria	Score*
Excellent	• IO or PO blood loss similar to or less (but not more than 20% greater) than expected for this type of procedure in a similar patient who does not have a bleeding disorder and who is undergoing the same surgical procedure. • No blood component transfusion is required or blood component transfusion similar to patient without a bleeding disorder is required • No IMP extradose needed	3
Good	• IO or PO blood loss that is greater than expected (but not more than 50% greater) for this type of procedure in a similar patient who does not have a bleeding disorder and who is undergoing the same surgical procedure. • No unexpected increased blood component transfusion requirement or blood component transfusion similar to patient without a bleeding disorder is required • No IMP extradose needed	2
Moderate	• IO or PO blood loss that is substantially greater than expected (more than 50% greater) for this type of procedure in a similar patient who does not have a bleeding disorder and who is undergoing the same surgical procedure, not explained by a surgical/medical issue other than hemophilia. • Additional blood component (within 2-fold greater than expected) transfusion is necessary • IMP extradose needed	1
Poor	• Uncontrolled IO or PO blood loss, not explained by a surgical/medical issue other than hemophilia, that requires intervention: o rescue therapy requirement o and/or increased blood component (>2-fold greater than expected) transfusion o and/or leads to unexpected hypotension or unexpected transfer to ICU	0

** A score assignment will be provided for efficacy assessment during the IO period, at 24 hours and 120 hours post-surgical wound closure. Given the rule in Section 4.2.1, an assessment score will have to 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.*

At screening, the surgeon (and other investigator where required) will communicate the predicted maximum blood loss in mL and the predicted maximum number of units and volume (mL) of blood component transfusions for the same procedure for a similar patient (i.e. patient of the same sex, age, and stature) without a bleeding disorder during:

- The IO period (from surgical incision until wound closure)
- The 24 hours PO period (from surgical wound closure until 24 hours post wound closure)
- The 120 hours PO period (from surgical wound closure until 120 hours post wound closure - cumulative prediction across the PO time, including the volume predicted for the 24 hours PO period)
- The subsequent days until D15 or hospital discharge if earlier.

At the surgical wound closure, the surgeon will determine the actual measurable blood loss and the actual number of units and volume of blood component transfusions during the IO period.

At 24 hours and 120 hours post-surgical wound closure, the investigator or designee will assess the actual measurable blood loss and the actual number of units and volume of blood component transfusions during the 24-hour PO period and during the 120-hour PO period, i.e. cumulative of the observations done at 24 hours post-surgical wound closure.

At each timepoint post 120 hours after surgical wound closure, the investigator or designee will assess the actual measurable blood loss and the actual number of units and volume of blood component transfusions.

Comments from the surgeon may be necessary if extenuating circumstances occurred (e.g. an artery was briefly severed and required additional time for surgical control of the bleeding creating a larger than predicted blood loss).

NOTE:

- The actual measurable volume of blood loss during the procedure (i.e. IO period) will be measured using the volume of drainage fluid and the volume of fluid on sponges and towels.
- When a drain is in place, the actual measurable volume of blood loss during the PO period will be measured by surgical drain output.
- A blood loss unambiguously resulting, as per investigator's judgement, from an accidental cause during the PO period should not be accounted for in the actual volume of blood loss taken into consideration in the assessment of the study treatment efficacy.
- The trigger for blood component transfusion based on whether Hb level will be Hb <7 g/dL (Carson et al., 2016[41]; Practice Guidelines for Perioperative Blood Management, 2015[42]; Liu et al., 2016[43]). When Hb is ≥7 g/dL and <8 g/dL, blood component transfusion will be allowed at investigator's discretion dependent on patient status.

9.2.2. Bleeding episodes at the surgical site

The number of bleeding episodes at the surgical site will be collected from surgical wound closure until last visit if any. For each bleeding, the reason for bleeding, the change in CCI treatment if any, the need for transfusion, the need for a surgical intervention/re-exploration, the failure to take CCI at recommended dose prior to physical therapy, etc will be collected.

9.2.3. Surgical interventions/re-explorations for bleeding

The number of surgical interventions/re-explorations due to bleeding will be collected between surgical wound closure and last visit if any. Note that the reason of bleeding should be collected.

9.2.4. Death from bleeding attributed to ineffective hemostasis

The number of deaths from bleeding attributed to due ineffective hemostasis will be collected between surgical wound closure and last visit if any. Note that the date, the time and the cause of the death should be collected.

9.3. Safety and Other Assessments

For each safety parameter, the investigator will determine whether it is considered as an AE. If assessed as an AE, the medical diagnosis (preferably), symptom, or sign, will be recorded on the AE page of the eCRF.

9.3.1. Physical examination

A physical examination will be performed at screening, within 24 hours prior to surgery, every 7±1 days from hospital discharge to last CCI dose for peri-operative management, at last CCI dose for peri-operative management, and at last visit.

It will be performed on the following body systems being described as normal or abnormal: general appearance, dermatologic, head-ears-eyes-nose-throat, endocrine system, lymph nodes, cardiovascular system, respiratory system, gastrointestinal system, musculoskeletal system, genito-urinary system, neurological system, psychiatric state.

Physical examination assessments will be recorded on the appropriate pages of the eCRF.

9.3.2. Vital signs

An assessment of systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (oral or tympanic) will be performed at screening, within 24 hours prior to surgery, every 24±4 hours from surgical wound closure to hospital discharge, every 7±1 days from hospital discharge to last CCI dose for peri-operative management, at last CCI dose for peri-operative management and at last visit.

Patients will rest for at least 3 minutes in the supine position before vital signs are assessed.

The weight will be measured at screening, within 24 hours before surgery and at last visit. The weight value measured within 24 hours before surgery will be used for calculating the dose of CCI throughout the whole treatment period.

The height will be measured at screening.

Vital sign values will be recorded on the appropriate pages of the eCRF. Unscheduled vital signs with clinically significant abnormalities according to the investigator will also be collected and recorded.

9.3.3. Clinical laboratory tests

The clinical laboratory tests are presented in Table 9–2. All test assessments will be performed at the local laboratories.

Table 9–2: 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
- 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*

All values will be recorded in the patient's medical file and the eCRF. Unscheduled laboratory values with clinically significant abnormalities according to the investigator will also be recorded.

9.3.3. 1. Viral serology tests

At screening, viral serology will be tested at the local laboratories:

- Hepatitis B surface antigen (HBsAg) by enzyme-linked immunosorbent assay for HBV
- anti-HIV 1 & 2 antibodies for HIV
- anti-HCV antibodies by polymerase chain reaction (PCR) for HCV

Patient serum samples will be collected the day of surgery before the first dose of CCI and at last visit and retained for long term storage for purposes of any safety evaluations deemed necessary in the future (e.g. antibodies evaluations). A laboratory manual will be provided to the investigator, the study nurses, and the local laboratory technicians where appropriate. It will describe the appropriate blood sample collection, processing, storage, and shipping procedures.

9.3.3. 2. Coagulation tests

The coagulation tests will consist of:

- FVIII or FIX, PT, and aPTT at screening
- AT III at screening only for patients with a history of treatment with fitusiran
- Fibrinogen, D-dimer at screening, within 24 hours prior to surgery, immediately after surgical wound closure [T0 (i.e. wound closure) and T8 hours], and every 24±4 hours from surgical wound closure to hospital discharge

9.3.3. 3. Hematology tests

The hematology tests will consist of:

- Hct, platelet count, RBC count, WBC count with differential at screening, within 24 hours prior to surgery and, at 24±4 hours after surgical wound closure, every 7±1 days from hospital discharge to last CCI dose for peri-operative management, at last CCI dose for peri-operative management, and at last visit
- Hb at screening, within 24 hours prior to surgery, every 24±4 hours from surgical wound closure to hospital discharge, then every 7±1 days from hospital discharge to last CCI dose for peri-operative management, at last CCI dose for peri-operative management, and at last visit
- CD4+ cell count at screening

9.3.3. 4. Chemistry tests

All chemistry tests, described in Table 9–2, will be performed at screening, at 24±4 hours after surgical wound closure, and at last visit.

9.3.3. 5. Urinalysis tests

All urinalysis tests, described in Table 9–2, will be performed at screening, at 24±4 hours after surgical wound closure, and at last visit.

9.3.3. 6. Inhibitor tests

The titer of inhibitors to FVIII (in hemophilia A patients) or FIX (in hemophilia B patients) will be assessed at screening. The Bethesda assay will be used for inhibitor testing.

9.3.4. Post-operative surgical site assessment

The PO surgical site assessment will be performed on all patients every 24±4 hours from surgical wound closure to hospital discharge, then every 7±1 days from hospital discharge to last dose of CCI for peri-operative management, at last CCI dose for peri-operative management, and at last visit. The assessment will include checking patient's incision or procedure site for inflammation, bleeding, infection, oozing, discoloration.

9.3.5. Electrocardiogram

A local 12-lead ECG will be performed at screening after the patient has rested in a supine position for at least 2 minutes. ECG will be described as normal or abnormal, and abnormality/ies specified.

Unscheduled 12-lead ECG with clinically significant abnormalities according to the investigator will also be recorded.

9.3.6. Prior and concomitant medication

Any medication(s) used during this study will be reviewed and recorded by the investigator or designee in the patient's medical file and the appropriate eCRF pages, including date and time of use, type of medication, route, dose, frequency, and indication.

Medications that will be forbidden prior to screening, before administration of CCI or surgery, or during this study are provided in Section 7.4.3.

9.3.7. Adverse events

Patients will be monitored for AEs/SAEs from informed consent/assent form signature to follow-up phone call planned 28±2 days after last visit. The investigator will ensure that all the AEs occurring during the study are identified and documented in the eCRF.

The identification of AEs may come from various sources:

- The investigator or a study nurse will closely monitor patients for any abnormal signs or symptoms throughout and immediately after IMP administrations.
- The investigator or a study nurse may clinically observe an AE in the patient at hospital.
- The patient may spontaneously report an AE to investigator or study nurse.
- From discharge to last visit, the patient will have to document on a patient's diary any AE that occurs outside the hospital and any medication taken. This diary will be verified at each visit by the investigator. The patient will be sensibilized to carefully report day and time of AEs. If the patient is too young to complete the diary himself, it will be completed by the parent(s)/legal representative(s). If information on the patient's diary is not clear, the investigator or designee will ask the patient or parent(s)/legal representative(s) questions. The investigator or designee may annotate the patient's diary but must date and sign the annotations.
- At each visit, the patient or his parent(s)/legal representative(s) should be questioned in a general way (without asking about the occurrence of any specific symptom) to ensure that no AE has been forgotten in the patient's diary.
- Vital signs at each visit (see Section 9.3.2)
- Physical examination and clinical laboratory tests (see Section 9.3.1 and Section 9.3.3); clinically significant abnormality in physical examination or biological tests performed at the screening as per study protocol could be regarded as a medical history if previously documented.
- Concomitant medications administered to the patient during participation in the study will be reviewed (see Section 9.3.6).
- Assessment for signs and symptoms of thromboembolic events performed from surgical wound closure until follow-up phone call, to include checking for any signs or symptoms of thromboembolic events, such as 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)
- Assessment for signs and symptoms of hypersensitivity reactions performed 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.
- PO surgical site assessment (see Section 9.3.4).

- Every 2 ± 1 days from hospital discharge to last CCI dose for peri-operative management and at 28±2 days after last visit, the investigator or a study nurse will call the patient, or his parent(s) or legal representative(s) in case of a minor patient, in order to collect information about the possible occurrence or the resolution or persistence of an AE after the patient has left the hospital. The purpose of this phone call will be to ensure that all AEs are tracked, even if the patient or his parent(s)/legal representative(s) do not complete the diary carefully. They will also be planned to discuss dosing regimen, ask about physical therapy visits, and remind for diary completion.
- If an AE is reported by the patient or his parent(s)/legal representative(s) during the phone call, the investigator will ask the patient or his parent(s)/legal representative(s) additional information at the next visit. If relevant; the investigator will report the AE in the eCRF.

It is the responsibility of the investigator to collect all the relevant information regarding identified AEs.

9.4. Adverse Events and Serious Adverse Events

9.4.1. Definition of adverse events

An AE is any untoward medical occurrence in patient to whom a medicinal product is administered. The occurrence does not have necessarily a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), any symptom or disease, whether new or exacerbated, temporally associated with the use of a medicinal product, whether or not related to the investigational drug product.

Events meeting the AE definition:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after the start of the study even though it may have been present before the patient's enrolment.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Pre-treatment or post-treatment events that occur as a result of protocol-mandated procedures (e.g. invasive procedures, modification of the patient's previous therapeutic regimen).
- Any abnormal laboratory test results (e.g. coagulation, hematology, biochemistry, urinalysis) or other safety assessments (e.g. vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator

Clinical significance is defined as any variation in physical or laboratory findings or any AE that has medical consequences that result in an alteration in the patient's medical care. Any laboratory value outside the normal range will be regarded as an AE if the investigator assesses the value as clinically significant.

Events NOT meeting the AE definition:

- Bleeding from surgical incision to the end of study
- Medical or surgical procedure (e.g. appendectomy): the procedure itself is not an AE, however, the condition that leads to the procedure is to be reported as AE.
- Planned major surgical procedure

The investigator is responsible for performing periodic and special assessments for AEs. The investigator and designee will note all AEs mentioned by the patient throughout the study. All clinical

complaints volunteered by or elicited from the patient during the study will be recorded in the patient's source documentation and on the appropriate page of the eCRF for the study period indicated. The patient will receive appropriate treatment and medical supervision for any AE that occurs.

Definition of SAE

An SAE is an AE that, at any time, fulfils one or more of the following criteria:

- Results in death
- Is life threatening, i.e. the patient was at immediate risk of death at the time of the event; it does NOT refer to an event which might have caused death if it was more severe
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, i.e. substantial disruption of a person's ability to carry out normal life functions
- Is a congenital anomaly/birth defect
- Is any important medical event that may not be immediately life threatening or result in death or hospitalizations but, based upon appropriate medical judgment, may endanger the patient or may require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a medicinal product is also considered an SAE.

Events initially reported as an AE may become serious. For example, diarrhea may become debilitating and require hospitalization or prolongation of hospitalization and is then reported as an SAE.

All SAEs will be summarized in the annual report or more frequently if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the eCRF as described in Section 9.4.5.

Definition of TEAEs

All AEs that occur at the time of or after the IMP administration until follow-up phone call will be regarded as TEAEs. All AEs occurring from informed consent/assent form signature up to (before) the IMP administration will be collected and will be referred to as non-TEAEs. AEs that are present before the IMP administration but subsequently worsen will be considered TEAEs.

9.4.2. Classification of an adverse event

9.4.2. 1. Severity of event

The investigator will assess the severity for each AE and SAE reported during the study based on his or her clinical judgment. AEs will be categorized for severity by the investigator according to the following definitions:

- Mild: symptom(s) barely noticeable to the patient, and/or does not make the patient uncomfortable. The AE does not influence daily performance or functioning. Medical intervention is not ordinarily needed for symptom(s) relief.

- Moderate: symptom(s) of a sufficient severity to make the patient uncomfortable. Performance of daily activities is affected. Treatment of symptom(s) may be needed.
- Severe: symptom(s) of a sufficient severity to cause the patient severe discomfort, and/or result in a marked impairment of function or may be life-threatening. Severity may cause cessation of treatment with IMP. Treatment for symptom(s) is given. The AE can produce sequelae, which also may require treatment, sometimes prolonged.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category used for rating the intensity of an AE (such as mild, moderate, or severe myocardial infarction). However, the AE itself may be of relatively minor medical significance, such as a severe headache. Both AEs and SAEs can be assessed as severe. An AE is considered serious when it meets one of the predefined outcomes described in Section 9.4.1.

9.4.2. 2. Relationship to IMP

The investigator must assess and record the IMP's relationship for any AE or SAE in source documents and the eCRF. For that purpose, the investigator will consider the time relationship between IMP administration and event occurrence; any expected IMP pharmacology; any potential role of the patient's underlying disease in the occurrence and/or timing of the event; and/or any other concomitant diseases, medical history, concomitant medications, or evolution of the event when IMP was withdrawn.

The IMP relationship criteria include the following:

- Related: The AE is known to occur with the IMP, there is a reasonable possibility that the IMP caused the AE, or there is a suggestive temporal relationship between the IMP and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the IMP and the AE.
- Not related: There is not a reasonable possibility that the administration of the IMP caused the event, there is no temporal relationship between the IMP and event onset, or an alternate etiology has been established.

Note: Causality assessment is based on available information at the time of the assessment of the event. The investigator may revise the causality assessment as additional information becomes available.

9.4.2. 3. Expectedness

The sponsor will be responsible for determining whether an AE is expected or unexpected.

An AE will be considered expected if the nature, severity, and outcome of the event are consistent with the reference safety information provided in the CCI IB for IMP.

9.4.3. Time period and frequency for event assessment and follow-up

Time period and frequency for event assessment:

To ensure complete safety data collection, recording and reporting, all (S)AEs occurring during the study, i.e. after informed consent/assent form signature until the follow-up phone call, must be recorded, even if no IMP was administered, including AEs occurring during the screening period and before the IMP infusion. These include all AEs occurring, recurring, or worsening after informed

consent/assent form signature. The period of observation for the study is from informed consent/assent form signature to the follow-up phone call. AEs should be captured even if they occur during periods without IMP treatment or during post-treatment periods.

If the investigator becomes aware, after that period, of any unusual safety information or any safety information that appears to be drug-related involving a patient who had participated in the study, even after the patient completes the study, he/she should contact the sponsor to determine how it should be documented and reported.

Follow-up of (S)AEs:

All AEs or SAEs assessed as not related to IMP, including clinically significant laboratory tests or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the end of study visit occurs, whichever comes first.

AEs or SAEs assessed as related to IMP will be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, or the patient is lost to follow up. If resolved, a resolution date should be provided.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the AE. This may include additional clinical laboratory testing or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient is withdrawn from study due to safety reasons, he/she should be followed until the event disappears, is otherwise explained or the patient's condition has stabilized.

Any patient who voluntarily withdraws from the study should be carefully questioned for the possible occurrence of an AE. Whenever possible, a patient should be followed through the last scheduled visit (i.e. 48 ± 4 hours after last CCI dose for peri-operative management) and the follow-up phone call (i.e. 28 ± 2 days after last visit) (see Section 8.2).

If no follow-up information can be provided after all efforts and attempts, the investigator must document the outcome as "unknown" and provide a justification in the source documents and in eCRF.

9.4.4. Adverse event reporting

When an AE or SAE occurs, the investigator is responsible for reviewing all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event(s). The investigator will record all relevant information about any AE (including SAEs) on the AE page of the eCRF.

The investigator will also attempt to report a diagnosis, instead of signs, symptoms, or other clinical information, for the AE. The diagnosis, not the individual signs and symptoms, should be documented on the appropriate page of the eCRF as the AE or SAE. In addition, SAEs need to be reported in the SAE report (see Section 9.4.5).

Each individual AE is to be listed as a separate entry on the AE eCRF form. The investigator will provide information on dates of onset and resolution, seriousness, severity, frequency, action(s) taken with regard to corrective therapy or to the IMP, outcome, and relationship to the IMP. The investigator must report to the sponsor or its representative all AEs that occur during the study from informed consent/assent form signature until the follow-up phone call or premature termination, regardless of their relationship to IMP. Apart from AEs clinically observed by the investigator, the patient will be

given the opportunity to report AEs spontaneously. A general prompt will also be given to detect AEs, e.g. “Did you experience any illness or unusual symptom since your last visit?”.

9.4.5. Serious adverse event reporting

The investigator will immediately, and no later than 24 hours after awareness, report to the sponsor or its representative any SAE, and must include an assessment of whether there is a reasonable possibility of a causal relationship between the IMP and the SAE.

If one or more seriousness criteria are fulfilled, the investigator must promptly forward to the sponsor or its representative a duly completed SAE report, even if the data are incomplete, but as soon as the minimum of following information is present:

- Identification of the notifying person
- Identification of the clinical study
- Identification of the patient (patient number)
- Description of the SAE and relationship to IMP
- Signature of the investigator

After the initial SAE report, the investigator is required to proactively follow each patient and to provide further information to the LFB Global PharmacoVigilance (GPV) on the patient’s condition. The investigator will ensure that follow-up includes any further investigations as may be indicated to elucidate the nature or the causality of the SAE. Patients who experience SAE are followed until the final outcome is known, even if this occurs after the end of the study follow-up. All AEs and SAEs assessed as related to IMP will be followed until the occurrence of one of the following:

- The condition resolves.
- The condition stabilizes.
- The AE or SAE is otherwise explained.
- The patient is lost to follow-up.

The appropriate report will be updated once the event resolves, stabilizes, or is otherwise explained or until the patient is lost to follow-up.

It is not acceptable for the investigator to send photocopies of the patient’s medical records in lieu of the properly completed SAE pages of the eCRF. Supporting documentation (discharge summaries, all examinations carried out, etc) will not be sent systematically, as all relevant information must appear and be summarized in the narrative of the SAE report. However, if judged important, the investigator could send these documents, or the sponsor could request them (all documents must be blinded with respect to the patient’s name). Any follow-up information must be reported to the sponsor within the same timelines as detailed below.

TIME FRAME

Initial SAE report		**Follow-up SAE** report	
Time Frame	**Documents**	**Time Frame**	**Documents**
IMMEDIATELY **and no later than 24 hours** as of awareness of the SAE	SAE report	**IMMEDIATELY** **and no later than 24 hours** as of availability of essential follow-up information	Updated SAE report

TRANSMISSION

Any SAE occurring after informed consent/assent form signature will be reported to the LFB GPV (± CRO Safety Department) via the eCRF system.

If reporting via the eCRF is not available, the SAE may be reported by email (pharmacovigilance@lfb.fr and MHGSafety@prahs.com, or in case of updated address during the study conduct, as instructed in the latest version in force of the Safety Management Plan and of the SAE/AESI rescue paper form) or fax (+33-1-69827325) to meet the reporting requirements. In case of reporting via email, the attached SAE report or SAE report follow-up should be encrypted (e.g. using 7-zip and a predefined password) to protect the confidentiality of the transmitted personal patient data. Details for reporting SAEs will be included in the safety information document.

Urgent reporting of SAEs is required for the following reasons:

1. To enable the sponsor to fulfill the reporting requirements to the appropriate regulatory authority

2. To facilitate discussion between the sponsor and the investigator about appropriate follow-up measures (if necessary)

3. To facilitate the sponsor's rapid dissemination of information about AEs to other investigators or sites in a multicenter study

4. To facilitate reporting unanticipated problems involving risk to patients to the IEC

Additionally, the IEC must be notified in writing of any suspected unexpected serious adverse reaction (SUSAR) reports or as required by the local IEC. It is the responsibility of the investigator or CRO to notify the IEC, according to local requirements.

If applicable, SAEs will be submitted to the appropriate regulatory agencies within the local regulatory timelines by the sponsor or designee. If the local regulations require submission through the investigator, the sponsor will facilitate this process.

SUSARs REPORTING

The sponsor will ensure that all relevant information about SUSARs are reported to the competent authorities and to relevant ethics committees in compliance to the Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical studies on medicinal products

for human use, and repealing Directive 2001/20/EC or the national regulatory requirements in all the participating countries.

9.4.6. Reporting events to participants

Not applicable.

9.4.7. Adverse events of special interest reporting

Other significant AEs considered as AESIs should be emphasized and continuously monitored for by the investigator. These AESIs are presented in Table 9–3.

Table 9–3: Adverse events of special interest

AESI category	Definition
Thromboembolic events	MedDRA HLGT: Embolism and thrombosis
Hypersensitivity reactions	Allergic/anaphylactoid and anaphylactic reactions MedDRA HLT: Allergic conditions NEC

Abbreviations: AESI, adverse event of special interest; HLGT, high-level group term; HLT, high-level term; MedDRA, medical dictionary for regulatory activities; NEC, not elsewhere classified

These events should be reported to the sponsor following the same process as SAE as described in Section 9.4.5.

9.4.8. Reporting of pregnancy

Not applicable as only male patients will be enrolled.

9.4.9. Reporting of overdose, misuse or medication error

9.4.9. 1. Definition

- **Overdose**

This refers to the administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorized product information. This shall also consider cumulative effects due to overdose.

- **Misuse**

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or within the legal status of its supply (e.g. without prescription for medicinal products patients to medical prescription).

- **Medication error**

This refers to any unintentional error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.

9.4.9. 2. Reporting

Occurrence of IMP misuse, overdose, or any medication error, whether or not associated to an AE, must be reported to the sponsor via the AE page of the eCRF. These special situations should be reported as SAEs only when fulfilling SAE criteria or associated with an SAE (see Section 9.4.5).

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Hypotheses

10.1.1. Primary efficacy endpoint

Denote by $\hat{p}$ the sample proportion corresponding to the primary efficacy estimand 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 and, at 24 and 120 hours after surgical wound closure. Scoring and determination of success is as described in Section 4.2.1.

The main null hypothesis to be tested for the primary efficacy estimand, i.e. proportion of successfully treated major procedures as defined above 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 favor 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 end of study analysis.

10.1.2. Secondary endpoints

No formal hypotheses will be evaluated for the secondary endpoints. Secondary endpoints will be summarized descriptively as provided in Table 10–1 and Section 10.4.3. As in the case of the primary efficacy endpoint, descriptive summary for each secondary endpoint will be presented as necessary at each evaluation timepoint, i.e. interim analysis, and end of study analysis.

10.2. Sample Size Determination

Given a true proportion of successfully treated major procedures of 0.75, a sample size of 17 evaluable procedures will yield a two-sided 96% 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 19 patients under a 1 procedure per patient setting.

10.3. Populations for Analyses

All efficacy analyses will be performed based on the full analysis set (FAS). FAS is defined as all major procedures conducted from patients enrolled into the study who had received at least one dose of study drug with each patient having one treated major procedure. The enrolled population consists of all patients 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.

Supportive analyses of the primary efficacy endpoint will be performed on both the FAS and PP populations. The 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. If the difference between FAS and PP population in terms of number of patients is not greater than 30%, then PP analysis will not be performed.

Safety analyses will be performed using the safety population (SAF). The SAF includes all patients who took at least one dose of CCI

10.4. Statistical Analyses

10.4.1. General approach

A statistical analysis plan (SAP) will be written to provide full details of the analyses (including interim analysis and final analysis), the data displays and the algorithms to be used for data derivations. Statistical analysis of all data will be performed using SAS® statistical software (SAS Institute, NC, USA).

Data collected in this study will be presented using summary tables, graphs, and patient data listings. Summary tables will present data by patient type (exposed to emicizumab or naïve to emicizumab), overall, and, if applicable, by time of collection. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum and maximum. Categorical variables will be summarized by frequencies and percentages. Graphs will be used to support the results presentation of the primary and secondary endpoints.

The SAP will include the definition of major or important protocol deviations and the link of major or important protocol deviations to the analysis sets. Major or important protocol deviations will be identified by clinically trained personnel before the study closure. The SAP will also quantify other characteristics for identification of the PP population, i.e. sufficiency of compliance to exposure to treatment and availability of measurements.

All means will be put in place to minimize missing data, especially for the primary efficacy endpoint (see Section 4.2.1 for replacement rule for a missing component score comprising the aggregate score) and the supportive hemostatic efficacy assessment at the IO and PO timepoints (i.e. attempt to collect replacement assessment within 12 hours of the scheduled assessment whenever feasible). Patients will be followed until the scheduled end of the study, independently of their adherence to the treatment schedule. Reasons for not completing key efficacy and/or safety assessments will be collected. Rules for imputation of missing assessments will be defined in the SAP.

10.4.2. Analysis of the primary efficacy endpoint

Analysis of the primary efficacy endpoint (see Section 10.1.1) will involve calculation of a point estimate and the associated Clopper-Pearson exact CI at each evaluation timepoint (i.e. interim analysis and end of study). This will be done based on total number of procedures as well as by patient type (exposed to emicizumab or naïve to emicizumab).

Calculation of point estimates and CIs based on the Clopper-Pearson method will also be performed using the PP population as supportive analysis if data permits.

In order to control for multiplicity, a 99% two-sided CI based on the 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 method will be calculated at final (end of study) analysis.

The primary efficacy estimand will be analyzed in terms of two intervention effect scenarios: effect based on study drug received and per definition of the full analysis population ignoring the occurrence of intercurrent events (intent to treat [ITT] treatment policy); and effect based on study drug received and per definition of the full analysis population with treatment response modified as failure in the presence of an intercurrent event indicative of adverse treatment effect (composite approach). Two intercurrent events were identified as material to the assessment of the efficacy of the study drug. These are withdrawal from assigned treatment and initiation of alternative/rescue therapy. Complete description of the analysis approach based on ICH E9 (R1) addendum framework will be provided in the SAP.

10.4.3. Analysis of the secondary endpoints

In general, analyses of the secondary endpoints (see Section 10.1.2) will involve the calculation of a point estimate together with the associated 95% CI. The calculated CIs will not be adjusted for multiplicity.

Analysis for each secondary efficacy endpoint is described in Table 10–1 below. Analysis of the rest of the secondary endpoints are described in Section 10.4.4.

Table 10–1: 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).
Proportion of successfully treated major procedures defined by a good or excellent hemostatic response based on the 4-point hemostatic scale 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 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)	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 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).

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

10.4.4. Safety analyses

All AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All medications (prior and concomitant) recorded as taken by the study patients will be coded using the World Health Organization Drug (WHODrug) dictionary. All laboratory values will be converted to SI (international system of units) and classified as normal, low, or high based on normal ranges supplied by the central laboratory.

The number and incidence of TEAEs, common TEAEs, treatment-emergent serious adverse events (TESAEs), TEAEs that led to study discontinuation, treatment-related TEAEs and treatment-emergent adverse events of special interest (TEAESIs), as well as observed and changes in clinical laboratory parameters and vital signs will be analyzed descriptively. AESIs include thromboembolic events and hypersensitivity reactions.

Summary results for AEs will be presented by MedDRA system organ class (SOC) and preferred term (PT) and will include stratification by relationship to CCI and severity as appropriate.

For clinical laboratory tests (including Hb level and coagulation-related parameters), vital signs and physical examination, descriptive statistics for the actual value at each timepoint and the change from

baseline (for continuous parameters) to each post-baseline timepoint will be tabulated; for discrete parameters, descriptive statistics for each response category shift from baseline to each post-baseline timepoint will be tabulated. Baseline is defined as the last measurement prior to study treatment. Shifts in key laboratory and vital sign parameters (using low, normal, and high classification) will be summarized from baseline to end of study. Proportion of patients with abnormal laboratory results and vital signs results will be summarized as well.

Medical history (number and incidence), prior and concomitant medications (number and incidence), common concomitant medications, procedure characteristics and exposure will be summarized descriptively. Summary results for medical history will be presented by MedDRA SOC and PT, while summary results for prior and concomitant medications will be presented by ATC Level 2 and ATC Level 4.

10.4.5. Baseline descriptive statistics

Demographic (age, sex, race, ethnicity, weight, height, and body mass index) and baseline characteristics, including disease characteristics for all patients will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

Details of the baseline characteristics will be provided in the SAP.

10.4.6. Planned 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 full analysis and PP populations and supportive secondary efficacy endpoints using the full analysis population. A 99% two-sided CI for the primary efficacy endpoint will be calculated based on the Clopper-Pearson exact method. Rules for stopping the study for efficacy or futility or continuing the study until the last planned patient to be enrolled has completed the study will be specified in SAP. The futility rule will be binding in order to help reduce the Type I error. Power and Type I error calculations using binomial distribution will be performed to further bolster the justification for the interim analysis rules and control of Type I error. 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 the number of observed failures is at least 4 then the study will be terminated for futility.

An external DMC in collaboration with an independent statistician will oversee the conduct of the analysis of interim data. The DMC will convene in accordance with rules and timelines established in the DMC charter and will make written recommendations as to whether to continue, modify or discontinue the study. The DMC will be provided with the safety data, to enable them to take an informed decision. Additionally, the DMC will review safety during conduct of the study. These recommendations will be submitted to LFB's internal Steering Committee (SC) for appropriate action. The role and responsibilities of the DMC and SC are described in the DMC charter.

10.4.7. Sub-group analyses

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

10.4.8. Tabulation of individual participant data

In general, all data will be listed and sorted by patient identification number and, when appropriate, by visit week/day within each patient. Patient profiles will be produced for purposes of data review and monitoring.

10.4.9. Exploratory analyses

Number of days in ICU and number of days in the hospital starting from the day of surgery until hospital discharge will be summarized descriptively. Mean number of days in ICU and mean number of days in the hospital and the associated CIs based on the t-distribution will be calculated. This will be done based on total number of procedures as well as by patient type (exposed to emicizumab and naïve to emicizumab).

11. SUPPORTING DOCUMENTATION AND REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

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

- Declaration of Helsinki
- Applicable International council for harmonisation (ICH) GCP adopted by the European Community
- Applicable local laws and regulations

11.1. Informed Consent/Assent Process

The process is described in Section 9.1.1. 1.

11.2. Study Discontinuation and Closure

The sponsor reserves the right to suspend or early terminate the study or site participation at any times but intends only to exercise this right for valid scientific or administrative reasons, or reasons related to patient safety and protection. Investigators will be notified in the event of study or site suspension or early termination.

Circumstances that may warrant suspension or termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Determination of futility

11.3. Confidentiality and Privacy

At patient level

Every effort will be made to maintain the pseudo anonymity and confidentiality of patients during this study. For this purpose, patients will be identified only by a patient number in all collected records (see Section 9.1.1. 2). They will be informed as to the strict confidentiality of their patient data, and

that their medical files may be reviewed for study purposes by authorized individuals other than their treating physician.

At study level

By conducting this study, the investigator affirms to the sponsor that all information regarding this study will be maintained in strict confidence. Such information can be communicated to the investigator's local ethics committee under an appropriate understanding of confidentiality.

11.4. Data Monitoring Committee

An external DMC is set-up for this study, as described in Section 10.4.6.

11.5. Clinical Monitoring

The investigator is responsible for the validity of all data collected at the site. The investigator should provide source documents that allow an accurate reporting and verification of all study information at the site. The sponsor is responsible for monitoring these data to verify that the rights and well-being of patients are protected, that study data are accurate (complete and verifiable to source data), and that the study is conducted in compliance with the protocol, GCP, and all regulatory requirements.

Monitoring visits to the study sites will be conducted periodically during the study according to the study monitoring plan to ensure that all aspects of the current, approved protocol are being followed. monitors will be given direct access to original source documents with due consideration to data protection and patient confidentiality. Source documents are original documents, data, and records from which the patient's eCRF data are obtained. The list of the source documents will be provided by the investigator. The monitors will have access to the eCRF to perform the Source Data Verification.

It is important that the investigator and relevant designee are available during monitoring visits and audits and that sufficient time is devoted to the process.

11.6. Quality Assurance and Quality Control

This study is sponsored by LFB BIOTECHNOLOGIES. The sponsor has delegated specific tasks regarding the conduct of this study to a CRO.

Quality control procedures as described in the Sponsor's Quality System as well as those of the CRO will be applied.

All quality control activities, including delegation of responsibilities between the sponsor and the CRO, will ensure patient safety and reliability of the clinical study data. The study sites may be audited by sponsor's clinical quality assurance auditor or designee. If an audit occurs, auditors will be given direct access to original source documents. Study sites will receive written notice in advance of any audit.

11.7. Data Handling and Record Keeping

11.7.1. Data collection and management responsibilities

Investigator

All clinical information required by the protocol must be entered on the eCRFs by authorized and duly trained study site personnel. Nevertheless, the investigator remains responsible for the accuracy, completeness and timeless of the data reported on the eCRF. The data reported on the eCRF should be consistent with source documentation.

In the source documents if edits to entries are required, the change must be performed in a manner that does not obscure the original entry. The identity of the person making the change and the date that the change is made must be noted.

The investigator will electronically sign the eCRF to validate the content.

Sponsor

Data management activities will be carried out by a CRO in accordance with GCP-ICH-E6.

The database will be created in electronic Data Capture system specifically validated and designed for clinical data management.

The patient data will be collected and entered into the eCRF by the investigator, or any other staff designated by the investigator in the delegation list.

Data processing, from data capture through database lock, will be carried out. As soon as a patient has given where applicable under local regulations her/his assent and the patient's parent(s) or legal representative(s) have signed the informed consent, the investigator will create the patient in the eCRF and will complete the appropriate form(s).

The consistency of data will be checked all along the study by computerized programs, manual data review and related queries will be generated in the data management system for resolution by the investigator.

Medical coding will be done using the most recent version of MedDRA for all medical terms (medical history, procedures, AEs...) and WHODrug for prior and concomitant medications.

Data cleaning, including ongoing data review, ongoing data validation, SAE reconciliation with the Pharmacovigilance database, reconciliation of all eCRF data, data coding review and quality controls will be done to ensure the overall quality, completeness and consistency of the database. In case of any identified discrepancies or missing data, appropriate corrective actions will be put in place.

At the end of the data handling process, a final data review meeting will be held to prepare the database lock. After the database lock, data will be transferred into SAS$^{(P)}$ format (version 9.4 or higher) to produce statistical analyses.

11.7.2. Study records retention

The investigators should retain all study-related documents in accordance with the applicable regulatory requirements of his/her country. These documents include but are not limited to signed protocol, eCRFs, informed consent/assent forms, IMP disposition records, safety reports, information regarding participants who discontinued, and other relevant documents and data. They should be kept together in the investigator site file provided to the investigator by the sponsor.

Sufficient information about the identity of all study patients, e.g. name, medical records number, patient number and study number, should be retained by the investigator so that any sponsor representatives, auditors or inspectors may access this information when required.

The investigator must retain all records until at least 2 years after the last approval of a marketing application in an ICH region for the IMP (CCI for the indication, which is being investigated, or at least 2 years have elapsed since the formal discontinuation of clinical development of CCI or 25 years after the database lock, whichever is longer, or longer if required by specific local regulations.

The investigator will contact the sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any of them. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

The investigator will also notify the sponsor should he/she relocate or move the study-related files to a location other than that specified in the sponsor's study master file.

All study-related documents should be kept in a secure area. In the cases of audit or inspection, they should be rapidly made available.

11.8. Protocol Deviations

Deviations from clinical protocol requirements will be reviewed and evaluated on an ongoing basis, and as necessary, appropriate corrective actions will be put into place.

Important and non-important protocol deviations will be identified and tracked on an ongoing basis throughout the study using a deviations management plan or equivalent and an appropriate tracking tool.

An important subset of protocol deviations is "important protocol deviations", which are defined by 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. For example, important protocol deviations may include enrolling patients in deviation of key eligibility criteria designed to ensure a specific patient population nor failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the trial". An example of an important protocol deviation provided in this Guideline is "deviations related to eligibility criteria, conduct of the trial, patient management, or patient assessment".

An analysis of important protocol deviations will be presented in the clinical study report to be written upon completion of this study and all related data-cleaning activities. It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations.

The principal investigator should have a process in place to ensure that the site staff or service providers delegated by the principal investigator/institution are able to identify the occurrence of a (suspected) serious breach to the regulation or to the version of the protocol applicable at the time of the breach. Serious Breach means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial. A (suspected) serious breach should be promptly, and no later than 24 hours, reported to LFB BIOTECHNOLOGIES, through the contact: seriousbreach@lfb.fr. Protocol deviations must be sent to the reviewing IEC / IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IEC / IRB requirements.

11.9. Publication and Data Sharing Policy

The study will be listed in the public applicable study registries required by site countries.

A clinical study report will be made available after the conclusion of the study. The final report may be submitted to relevant regulatory authorities to support a request for product registration. It is the intention of the sponsor to publish the results of this study in a peer-reviewed journal.

The investigator will provide any patient who so requests it with the overall results of the study, once it is completed, according to local requirements. The sponsor will provide the investigator with the overall results beforehand.

11.10. Financial Disclosure

All rules and regulations on the documentation and disclosure of any potential financial conflicts will be followed.

11.11. Additional Considerations

Not applicable.

11.12. Protocol Amendment History

Amendment	Affected sections	Description of Change	Brief Rationale
1	1.1, 4.2.2, 9.1.2, 9.3.3 & Tables 1-1, 4-1 and 9-2	Removal of a coagulation test	Prothrombin fragment 1+2 testing requirement removed because unfeasible in most sites and its purpose is already fulfilled by D-dimer testing
1	2.2	Extension of IMP shipment temperature conditions	Alignment of shipment temperature conditions with IMP storage conditions, thus extending possible shipment conditions to ambient temperature.
1	Cover page	Administrative changes	Addition of EUDRACT number

2	Definitions for the specific purpose of StudyF7TG2202 & References List	Revision of the definition of major surgical procedure	Alignment with definition adapted from Santagostino et al. (2015) and inclusion of multiple simultaneous dental extractions as per Solimeno et al's review (2018)
2	6 and 6.1	Revision of inclusion criterion no. 2	Eligibility extension to patients with history of high titer of inhibitors to factor concentrates even if no anamnestic response was documented, because those patients are expected to present an anamnestic response in case of new exposure to those factors while unethical to put them at such a risk.
2	9.1.1.3 and 9.1.2.1	Removal of the enrolment committee contact details from the protocol	Avoid further protocol amendents in case of change in membership
2	9.2.1	Clarification about actual blood loss for consideration in efficacy assessments	Guidance on how to consider a blood loss unambiguously resulting, as per investigator's judgement, from an accidental cause during the post-operative period
2	Cover page, Investigator's Agreement, Coordinating Investigator's Agreement, Summary of changes, 1.1, 1.2, 2, 6.2, 7.5, 9.3.2, 10.3, 10.4.6, 11.4, 11.6, 11.8, 11.11 and 11.12	Administrative changes	Implementation of changes from new protocol template, rewording of confusing sentences, alignment between synopsis and body of protocol, updates, formatting and typographical corrections

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13. APPENDICES

13.1. Global Hemostatic Response

The Table 13–1 presents the global hemostatic response based on the individual scores at three timepoints.

Table 13–1: 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		
0 or M	1	3		
0 or M	1	2	0-4 (with at least one individual score = 0 or missing (without a replacement score) [M])	POOR
0 or M	0 or M	3		
2	0 or M	0 or M		

Individual scores			Global hemostatic response score*	Global hemostatic response
Intra-operative	24 hours post-operative	120 hours post-operative		
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 Section 4.2.1.*