Clinical Trial Protocol: LFB-FVIIa-008-14

Study Title:	A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)
Study Number:	LFB-FVIIa-008-14
Study Phase:	Phase 3
Product Name:	LR769
Indication:	LR769 is intended to be used for the on-demand treatment of bleeding episodes and for the prevention of excessive blood loss and achievement of hemostasis in surgery or other invasive procedures in patients with congenital hemophilia A or B with inhibitors to coagulation factors VIII or IX
Investigators:	Multicenter, multinational study
Principal Investigator:	Miguel A. Escobar, MD University of Texas Health Science Center Houston, TX
EudraCT #:	2015-000957-19
IND #	15183
Sponsor:	LFB USA Inc.
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Original Protocol:	02 September 2015
Amendment 1	14 December 2015
Amendment 2	18 February 2016
Amendment 3	03 August 2016
Amendment 4	20 December 2016

SYNOPSIS

Sponsor: LFB USA Inc.
Name of Finished Product: LR769
Name of Active Ingredient: Coagulation Factor VIIa (Recombinant)
Study Title: A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)
Study Number: LFB-FVIIa-008-14 (Protocol Amendment 4)
Study Phase: Phase 3
Primary Objective(s): • To assess the efficacy of LR769 to prevent excessive bleeding and to achieve hemostasis in hemophilia A or B patients with inhibitors to factor VIII (FVIII) or factor IX (FIX) undergoing elective surgical or other invasive procedures.
Secondary Objective: • To assess the safety of LR769 including the immunogenic potential of the drug product.
Study Design: This is an international, multicenter, single-arm, Phase 3 study. Patients aged 6 months to 75 years, inclusive, who have congenital hemophilia A or B with inhibitors and who are scheduled for an elective surgical or other invasive procedure will be enrolled. Different age restrictions may apply per local regulation and ethical considerations; enrollment of children <12 years of age will not begin until after review of data from the PERSEPT 2 study by the DMC. After obtaining Informed Consent from the patient and/or the patient's parent(s)/legal guardian(s), patients who are scheduled for an elective surgical or other invasive procedure will have screening assessments performed to determine eligibility. Patients who are or were participating in another LR769 study (eg, PERSEPT 2) and who meet all eligibility criteria will be allowed in this study if the study is open for enrollment in that age group. Safety follow up will continue until 28 (±3) days after the last dose of LR769.

Intraoperative Efficacy Assessments

Immediately after completion of the procedure, the surgeon or practitioner performing the procedure will assess the intraoperative efficacy of LR769. The patient's intraoperative response to treatment with LR769 will be assessed by the surgeon/practitioner and recorded as "excellent," "good," "moderate," or "poor."

Postoperative Efficacy Assessments

Efficacy assessments will be completed every 24 (±2) hours and at last administration of LR769. The patient's postoperative response to treatment with LR769 will be assessed by the investigator or designee and recorded as "excellent," "good," "moderate," or "poor." If the patient is discharged while on treatment, these assessments will be done via telephone. The final assessment (which represents the primary efficacy outcome) will be performed by the investigator at the study center 48 (±4) hours after last dose of LR769 and will be based upon the totality of assessments performed on the patient at each timepoint.

Safety Assessments

Patients will be assessed for safety throughout the study via physical examinations, assessments for thromboembolic events, postoperative assessments, clinical safety laboratory tests, vital signs, immunogenicity tests, and the recording of adverse events (AEs).

Study Population:
Patients, aged 6 months to 75 years, inclusive, who have congenital hemophilia A or B complicated by high titer inhibitors (peak Bethesda Units [BU] ≥5). Some patients may have low levels of inhibitors (i.e., BU<5) but still cannot be treated with factor VIII or factor IX concentrates since these patients are known to have high-responding inhibitors, manifested by an anamnestic response (defined as a peak titer >5 BU after re-exposure to factor concentrates); or, if not demonstrating an anamnestic response, remain refractory to increased dosing with factor concentrates. Therefore, these patients cannot be treated with these products but may be included in this study if they are scheduled for an elective surgical or other invasive procedure. Detailed medical history will be obtained for these patients to document the high-responding features of their inhibitors. Both major and minor surgical or other invasive procedures are allowed in the study.

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. a positive inhibitor test BU ≥5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally), OR
   b. an inhibitor test BU <5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally) but expected to have an anamnestic response to FVIII or FIX, as demonstrated by a history of a high-responding inhibitor manifested by a previous anamnestic response (defined as a peak inhibitor titer >5 after re-exposure to factor concentrates), precluding the use of FVIII or FIX products to treat or prevent bleeding, OR
   c. an inhibitor test BU <5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally) but expected to be refractory to FVIII or FIX, as demonstrated by the patient's history of previous failure to respond to FVIII or FIX concentrates, even in the absence of a documented anamnestic response, precluding the use of FVIII or FIX products to treat or prevent bleeding episodes
3. be ≥6 months to ≤75 years of age; different age restrictions may apply per local regulation and ethical considerations (enrollment of children <12 years of age will not begin until after review of data from the PERSEPT 2 study by the DMC)
4. be scheduled for an elective surgical or other invasive procedure
5. be capable of understanding and willing to comply with the conditions of the protocol OR in the case of a patient <18 years of age, parent(s)/legal guardian(s) must be capable of understanding and willing to comply with the conditions of the protocol
6. have read, understood, and provided written Informed Consent (patient and/or parent(s)/legal guardian(s) if the patient is <18 years of age) or Assent, if applicable

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 counts at screening should be >200/µL)
3. known intolerance to LR769 or any of its excipients
4. currently receiving immune tolerance induction (ITI) therapy
5. have a known allergy or hypersensitivity to rabbits
6. have a platelet count <100,000/µL
7. have received an investigational drug within 30 days of the planned first LR769 administration , or is expected to receive such drug during participation in this study (with the exception of patients who are or were participating in another LR769 study,

e.g., a study assessing the treatment of bleeding episodes with LR769)

8. 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)
9. have a history of arterial and/or venous thromboembolic events (such as myocardial infarction, ischemic strokes, transient ischemic attacks, deep venous thrombosis [DVT] or pulmonary embolism [PE]) within 2 years prior to the planned first dose of LR769, uncontrolled arrhythmia, or current New York Heart Association (NYHA) functional classification score of stages II – IV
10. have an active malignancy (those with non-melanoma skin cancer are allowed)
11. 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 trial participation or trial outcome (eg, a history of non-responsiveness to bypassing products)
12. 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 LR769
13. have active gastric or duodenal ulcer disease

Test Product, Dose, and Mode of Administration:
LR769 (Coagulation Factor VIIa (Recombinant).

Initial Treatment: For a minor elective surgery or other minor invasive procedure, a dose of 75 µg/kg of LR769 administered within ≤2 minutes will be used as the initial dose; for a major elective surgery or other major invasive procedure, a dose of 200 µg/kg of LR769 administered within ≤2 minutes will be used as the initial dose before the surgical incision or start of an invasive procedure. For both minor and major procedures, administration will be repeated no more frequently than every 2 hours (±5 minutes) at a dose of 75 µg/kg during and after surgery or invasive procedure.

If the patient requires further treatment with LR769 after hospital discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines specified below; however, the efficacy assessment will be completed by the investigator or designee every 24 (±2) hours and at last administration of LR769 via telephone. The assessment at 48 (±4) hours after the last dose of LR769 will be performed by the investigator at the study center. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769 administration.

If physical therapy is planned, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended each time before the therapy begins. Similarly, before drain or suture removal, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended.

Major Surgical Procedures

Major surgical procedures are those that usually require ≥5 days of factor replacement in hemophilia patients with inhibitors and typically involve entry into a body cavity and/or organ removal or similarly complex procedures. These include, but are not limited to, the following: abdominal (eg, cholecystectomy, bowel resection, appendectomy), thoracic (eg, lobectomy, mediastinal procedures), orthopedic (eg, spinal, hip and knee surgery, joint replacements, synovectomy), genitourinary (eg, prostate resection, non-endoscopic bladder surgery), neurological, and cosmetic/reconstructive surgery (eg, facelift, burn scar surgery).

Placement of a central venous access device may qualify as a major surgical procedure if the complexity of the procedure and patient, based on the investigator's judgement, require ≥5 days of coagulation factor replacement.

Treatment for Major Surgical Procedures: The initial dose of LR769 (200 µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours after completion of the procedure. The minimum duration of LR769 treatment for major procedures will be 5 days, according to the frequency listed in the table below.

Dose(s) and Dosing Schedule(s) for Major Surgical Procedures

Day	Dose	Recommended Frequency
Day 0 (within 2 minutes of surgical incision or invasive procedure)	200 µg/kg	Initial dose
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes)
Days 3-4	75 µg/kg	Intervals of up to every 4 hours but not more frequently than every 2 hours
Days 5-6	75 µg/kg	Intervals of up to every 6 hours but not more frequently than every 2 hours
Days 7-10	75 µg/kg	Intervals of up to every 8 hours but not more frequently than every 2 hours
Day 11 to Last Administration of LR769	75 µg/kg	Intervals of up to every 12 hours but not more frequently than every 2 hours

The patient will be followed postoperatively according to the site's standard of care.

NOTE: If clinically indicated because of oozing or similar findings suggesting the need for more frequent LR769 infusions, the treatment interval may be shortened in consecutive doses within the guidelines above.

Minor Surgical or Other Invasive Procedures

Minor surgical or other invasive procedures typically require <5 days of factor replacement and usually involve the skin, mucous membranes, or superficial connective tissue and include, but are not limited to, the following: placement of a PICC or other central venous access device, isotopic synovectomies, tooth extractions, and skin biopsies. Patients who are about to undergo invasive procedures, including lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy are allowed in the study as well; these are also regarded as minor procedures.

Treatment for Minor Surgical or Other Invasive Procedures: The initial dose of LR769 (75 µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours**.** The minimum duration of LR769 infusion for minor procedures will be 2 days, according to the frequency listed in the table below, except for certain procedures that may not require this duration of treatment to achieve hemostasis as noted below.

Dose(s) and Dosing Schedule(s) for Minor Surgical or Other Invasive Procedures

Day	Dose	Recommended Frequency
Day 0 (within 2 minutes of surgical incision or invasive procedure)	75 µg/kg	Initial dose
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes) initially. Interval may be increased upon the investigator's judgment
Day 3 to Last Administration of LR769	75 µg/kg	Intervals of up to every 24 hours but not more frequently than every 2 hours

For less invasive procedures, such as PICC or Port-a-Cath placement and for procedures such as dental extractions, the patient may be treated for ≤48 hours if the investigator or designee determines this shorter duration of treatment is sufficient to achieve hemostasis.

NOTE: If clinically indicated because of oozing or similar findings suggesting the need for more frequent LR769 infusions, the treatment interval may be shortened in consecutive doses within the guidelines above.

For all procedures: Discharge and Follow up

If the patient requires further treatment with LR769 after the outpatient procedure or hospital discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines specified for both major and minor surgical or other invasive procedures. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769

administration.

Reference Therapy; Dose; and Mode of Administration:

No reference therapy will be used.

Duration of Treatment:

For major surgeries, treatment with LR769 will be for ≥5 days; for minor surgeries, treatment will typically be for ≥2 days, though for some less invasive procedures (eg, dental procedures), ≤48 hours treatment may be appropriate based on the investigator's judgment. The duration of treatment will be the time required to achieve and maintain adequate hemostasis based on the investigator's judgment.

Duration of Study:

The study will continue until at least 12 surgical procedures (including a minimum of 6 major surgeries, of which at least 5 must be procedures other than central venous access device placement) have been performed in at least 6 patients.

Efficacy Assessments:

Intraoperative Assessment of Efficacy by Surgeon or Practitioner Performing the Procedure

Efficacy of treatment with LR769 intraoperatively will be assessed by the surgeon/ practitioner immediately after completion of the procedure and recorded based on the following parameters:

- Estimated blood loss in the surgical patient as compared to the maximum expected volume of blood loss in a patient without a bleeding disorder;
  - Prior to surgery, the surgeon/practitioner will note if the procedure is major or minor and the type of anesthesia that is planned, and estimate the maximum expected volume of blood loss based upon the type of surgery and the surgeon/practitioner's previous experience in a patient who does not have a bleeding disorder. After the procedure, the surgeon/practitioner will determine the actual characteristics of the procedure and estimate the volume of blood lost during the procedure using the following factors as a guide: volume of drainage fluid, volume of fluid on sponges and towels, etc. The maximum expected volume of blood loss and the estimated volume of blood loss during the procedure will be recorded.
  - The surgeon/practitioner will assess the intraoperative hemostasis by comparing the estimated intraoperative blood loss with the maximum expected blood loss estimated prior to the procedure as well as the amount of fluid replacement given, transfusion requirements, hemodynamic stability, etc.
- Comments from the surgeon/practitioner may be necessary if extenuating circumstances occurred (eg, an artery was briefly severed and required additional time for surgical control of the bleeding creating a larger than expected blood loss)

Taking into account the above parameters, intraoperative response to treatment will be rated as follows:

- Excellent: intraoperative blood loss similar to or less than expected for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no blood component transfusion is required

- Good: intraoperative blood loss that is greater than expected (but not more than 50% greater) for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no unexpected increased blood component transfusion requirement
- Moderate: intraoperative blood loss that is substantially greater than expected (more than 50% greater) for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; additional blood component (within 2-fold greater than expected) transfusion is necessary
- Poor: uncontrolled intraoperative blood loss, not explained by a surgical/medical issue other than hemophilia, that requires intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or leads to hypotension or unexpected transfer to Intensive Care Unit [ICU])

Investigator or Designee Assessment of Hemostasis on Postoperative Days

The investigator or designee will make postoperative efficacy assessments at 24 (±2) hours after procedure completion, at 24 (±2) hour intervals while treatment with LR769 is ongoing, after the last dose of LR769, and during follow-up visits. The final assessment (which represents the primary efficacy outcome) will be performed by the investigator at the study center 48 (±4) hours after the last dose of LR769 and will be based upon the totality of the assessments performed on the patient at each timepoint also taking into consideration the surgeon/practitioner's intraoperative hemostatic assessment, the number of (interventions for) bleeding episodes, oozing, blood transfusions, and the amount of LR769 used. All assessments will be recorded in the patient's record.

Postoperative response to treatment will be rated as follows:

- Excellent: postoperative blood loss similar to or less than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no blood component transfusion is required
- Good: postoperative blood loss greater than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; no unexpected need for blood component transfusion
- Moderate: postoperative blood loss that is substantially greater than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; additional blood component [within 2-fold greater than expected] transfusion is necessary
- Poor: uncontrolled postoperative blood loss, not explained by a surgical/medical issue other than hemophilia that requires intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or leads to hypotension or unexpected transfer to Intensive

Care Unit [ICU])

Safety Assessments
Safety of treatment with LR769 will be assessed by the following:

- Physical examinations at screening, pre-procedure and 48 (±4) hours after last dose of LR769
- Assessment for signs and symptoms of thromboembolic events every 24 (±2) hours from completion of the procedure until 48 (±4) hours and 28 (± 3) days after last dose of LR769, to include checking for any signs or symptoms of thromboembolic events, 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)
- Postoperative assessment performed on all patients while hospitalized every 24 (±2) hours from completion of the procedure until 48 (±4) hours after last dose of LR769 (unless discharged from the hospital sooner) to include checking patient's incision or procedure site for inflammation, bleeding, infection, oozing, discoloration
- Clinical safety laboratory tests (chemistry, hematology and urinalysis) at screening, 24 (±2) hours after completion of the procedure, and during follow up
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) at screening, just prior to the surgical or other invasive procedure, 24 (±2) hours after completion of the procedure, and follow up at 48 (±4) hours after last dose of LR769
- Electrocardiogram (ECG) at screening
- AEs recorded throughout the study
- Immunogenicity of LR769 at pre-procedure and during follow-up visits

Statistical Methods:
All data collected in this study will be displayed using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

Analysis Populations:

The Efficacy Population is defined as all patients who receive LR769 treatment, undergo a surgical or invasive procedure, and have at least 1 efficacy assessment. The Safety Population is defined as all patients who receive at least 1 dose of LR769. All efficacy analyses will be performed on the Efficacy Population and all safety analyses will be performed on the Safety Population.

Sample Size Determination:

The sample size was determined based on adaptations of international guidelines for coagulation factors and after US and EU health authority consultations.

Efficacy Evaluations:

Primary efficacy endpoint:

- Percentage of surgical or other invasive procedures with a "good" or "excellent" response to LR769 treatment 48 (±4) hours after the last administration of LR769 as assessed by the investigator.

A point estimate of this endpoint will be calculated together with a Clopper-Pearson exact 95% confidence interval.

Secondary efficacy endpoints:

- Percentages of success as defined as the combination of "good" and "excellent" responses by the investigator or designee for all efficacy timepoints other than the primary
- Percentages of "poor," "moderate," "good," and "excellent" response by the investigator or designee for all efficacy timepoints
- Percentages of success as defined as the combination of "good" and "excellent" responses by the surgeon/practitioner
- Percentages of "poor," "moderate," "good," and "excellent" response by the surgeon/practitioner for the intraoperative period
- Intraoperative blood loss determined by the surgeon/practitioner as compared to the surgeon/practitioner's maximum predicted blood loss
- Number of events requiring transfusion between start of procedure and 48 (±4) hours after last administration of LR769
- Changes in hemoglobin between start of procedure and 48 (±4) hours after last administration of LR769
- Amount of LR769 used. Total, and separated by use in hospital, at home, or for specific reasons (eg, physical therapy, or other reasons like drain or suture removal)
- Number and type of bleeding episodes at the surgical site between start of procedure and 48 (±4) hours after last administration of LR769
- Number of surgical interventions/re-explorations for bleeding episodes between start of procedure and 48 (±4) hours after last administration of LR769

Point estimates will be computed together with 95% confidence intervals for the proportion of successes, mean difference between intraoperative blood loss and surgeon/practitioner's maximum predicted blood loss, proportion of events requiring transfusion, mean hemoglobin level at each time point, mean number of bleeding episodes, mean amount of LR769 used, and mean number of surgical interventions/re-explorations for bleeding episodes. Clopper-Pearson exact confidence intervals will be used for dichotomous endpoints; confidence intervals for continuous variables will be based on the normal approximation.

Safety Evaluations

Safety endpoints include the following:

- Analysis (including relationship to LR769, severity, and outcome) of AEs/SAEs between first LR769 administration and 28 (±3) days after last administration of LR769
- Analysis of treatment-emergent thromboembolic events between start of procedure and 28 (±3) days after last administration of LR769
- Analysis of allergic and anaphylactic reactions between start of procedure and 28 (±3) days after last administration of LR769
- Analysis of treatment-emergent antibodies against LR769 or host-related impurities between start of procedure and 28 (±3) days after last administration of LR769

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). The number and percentage of patients with any treatment-emergent AEs (TEAEs) and any treatment-emergent serious AEs (SAEs) will be presented for all patients. The number and percentage of patients with any treatment-emergent thromboembolic event and/or allergic and anaphylactic reactions will be presented for all patients.

For vital signs and clinical laboratory test results, descriptive statistics for the actual value at each timepoint and the change from baseline to each post baseline timepoint will be tabulated. Descriptive statistics for immunogenicity data will also be produced for the specified timepoints. Two-sided paired t-tests will be used to test whether the mean changes from baseline equal 0. Baseline is defined as the last measurement prior to study treatment.

Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for the oversight of patient safety. The DMC will consist of 3 specialists in the care of hemophilia patients. DMC members will be independent of the study and Sponsor. During the course of the study, the DMC will review immediate serious adverse drug reactions and quarterly review of SAE listings. In addition the DMC will review the data and recommendation from the DMC in the PERSEPT 2 pediatric study to determine when enrollment of patients <12 years of age is appropriate for this study.

Date of Original Approved Protocol: 02 September 2015

Date of Protocol Amendment 2: 18 February 2016

Date of Protocol Amendment 3: 03 August 2016

Date of Protocol Amendment 4: 20 December 2016

Date of Most Recent Protocol Amendment (if applicable): Not applicable

Prepared in: Microsoft Word 2010

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AA	amino acid
AE	adverse event
ALB	albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase (SGOT)
BU	Bethesda Units
BUN	blood urea nitrogen
Ca	calcium
CRO	contract research organization
CT	computed tomography
DMC	Data Monitoring Committee
DVT	deep venous thrombosis
eCRF	electronic case report form
ECG	electrocardiogram
EGF	epidermal growth factor
EMA	European Medicines Agency
EOT	last administration of LR769
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
HC	heavy chain
Hct	hematocrit
HCV	hepatitis C virus
HEENT	head, ears, eyes, nose, throat
Hgb	hemoglobin
HIV	human immunodeficiency virus
hr	hour
HTRS	Hemophilia and Thrombosis Research Society
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ICU	intensive care unit
IRB	Institutional Review Board
ITI	immune tolerance induction
K	potassium
LC	light chain
LDH	lactic acid dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
Na	sodium
NSAID	non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
Pd	plasma-derived
PD	pharmacodynamic(s)
PE	pulmonary embolism
PICC	peripherally inserted central catheter
PK	pharmacokinetic(s)
PT	prothrombin time

PT	preferred term
RBC	red blood cell (count)
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	system organ class
TF	tissue factor
US	United States
WBC	white blood cell (count)

1 INTRODUCTION

LFB is developing an activated recombinant human factor VII (LR769) protein produced in and purified from the milk of transgenic rabbits, selected for the production of this complex human glycoprotein.

1.1 Congenital Hemophilia

LR769 is produced by recombinant DNA technology employing site-directed expression of the human factor VII (FVII) gene in the mammary gland of genetically engineered rabbits. The transgene containing the human factor VII 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 factor VII 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.

Hemophilia is an inherited coagulation disorder due to deficiency of either factor VIII (FVIII; hemophilia A) (Patek and Taylor, 1937) or factor IX (FIX; hemophilia B) (Biggs, 1952). Reported prevalence of hemophilia is approximately 2 in 10,000 males globally, and prevalence in developed countries has been reported as approximately 1 in 10,000 males (Stonebraker et al., 2010). Hemophilia A is the most common form, with the prevalence of hemophilia B being one-fifth that of hemophilia A. Virtually only males are affected with the congenital form of hemophilia as both the FVIII and FIX genes are located on the X-chromosome.

Severe hemophilia can cause serious bleeding problems in babies. Therefore, children who have severe hemophilia usually are diagnosed early in life. People who have milder forms of hemophilia may not be diagnosed until they are adults.

Treatment of hemophilia A and B patients is usually with anti-hemophilic FVIII or FIX products, replacing the deficient factor. However, the development of inhibiting antibodies to FVIII and FIX is an ongoing concern. Individuals with severe hemophilia A develop inhibitors more often (20% to 30%) than those with hemophilia B (<5%) (Astermark, 2006), though the reasons why are unclear. People who have more severe hemophilia, a family history of inhibitors, certain genetic mutations, and minorities with hemophilia are at a higher risk of developing inhibitors. In patients who have developed inhibitors, these may disappear again over time. This is due to the spontaneous disappearance of low-titer inhibitors and the eradication of inhibitors with immune tolerance induction (ITI) therapy (Astermark, 2006). The *prevalence* of inhibitors to FVIII or FIX is therefore much lower than the lifetime risk for inhibitors and is in the range of 5% to 8%. Inhibitors may occur at any time in a patient's life, but the majority of patients develop inhibitors early in life after a median of 10 exposure days. It is rare to develop inhibitors after >150 exposure days (Hay et al., 2006). The inhibitor titers are usually given in Bethesda Units (BUs), where one BU is defined as the

amount of antibody that neutralizes 50% of FVIII or FIX in normal plasma (Astermark, 2006).

Inhibitors are also classified as high- or low-responding based on the titers found. Low responders are those who have a persistently low inhibitor titer of <5 BU despite repeated challenge with substitution factor concentrate, i.e., no anamnestic response. High responders are those who reportedly have a consistently high titer of ≥5 BU or had this in the past after re-exposure (high anamnestic response) with consequently an inability to treat hemorrhage with factor concentrates (White et al., 2001). A small group of patients also exist who have a constantly low inhibitor titer (<5 BU), but still do not respond sufficiently to (increasing doses of) FVIII or FIX treatment. Since replacement therapy with the missing coagulation factor is ineffective in patients with inhibitors, bypassing agents are commonly used to stop a bleeding episode in patients with inhibitors. Treatment with the activated form of factor VII (FVIIa) provides a way to bypass the need for FVIII or FIX and initiates clotting at a bleeding site. Thrombin (factor IIa) generation under normal circumstances is driven by the formation of FXa from FX by the complex of FVIIIa and FIX (via the intrinsic pathway).

FVIIa can either be provided by administration of plasma-derived activated prothrombin complex concentrate (aPCC, or *factor eight inhibitor bypassing agent*, FEIBA®) or by administration of factor VIIa concentrate, either plasma-derived or recombinant (currently available as NovoSeven®).

Results from the Hemophilia and Thrombosis Research Society (HTRS) registry indicate that FVIIa was effective in approximately 90% of joint bleeding episodes (Valentino et al., 2009). A study looking at home treatment with 90 µg/kg of NovoSeven® every 3 hours up to 3 times showed 92% of bleeding episodes (including joints, muscle, and mucocutaneous bleeding episodes) responded well (Key et al., 1998). The dosing regimen for treatment of bleeding episodes is dependent on the type and severity of the bleeding, but usually 90 µg/kg administered every 2 to 3 hours is effective (NovoSeven® SmPC). Higher doses (eg, 270 µg/kg) may also be utilized for treatment of mild/moderate bleeding episodes.

Surgery in patients with hemophilia and high-titer inhibitors is challenging as bypassing products are required and there is no direct measure, such as a factor level, to monitor hemostasis (Shapiro and Cooper, 2012). Treatment varies in patients with hemophilia based on inhibitor status and surgical procedure (Shapiro, 2014). This makes management of bleeding episodes difficult and poses a particular therapeutic challenge for elective or emergency surgical procedures (Shapiro et al., 1998). For these reasons this study is focusing on planned elective procedures and using assessments of hemostasis at completion of procedure and at multiple postoperative timepoints.

For patients with inhibitors, only 2 randomized trials have been performed to investigate postoperative hemostasis: one compared 2 doses of rFVIIa and the other compared bolus and continuous infusion of rFVIIa. These studies documented that elective surgery, including orthopedic interventions, was feasible in patients with inhibitors (Shapiro, 2014). In addition, consensus panels have published guidelines for surgical procedures in patients with inhibitors, though these guidelines largely focus on maximizing short-term hemostatic

outcomes and minimizing the potential for complications immediately after surgery (Escobar et al., 2012;Giangrande et al., 2009;Teitel et al., 2009).

Short-term prophylactic treatment is typically given to hemophilia patients with inhibitors before they undergo surgical procedures or for example, tooth extractions, or insertion of venous access devices. Arthropathy is very prevalent in hemophilia patients and orthopedic surgery, including joint replacements is relatively frequent. Recombinant FVIIa has been used successfully in these major surgical procedures (Obergfell et al., 2008;Takedani et al., 2010). FVIIa is also used for other bleeding disorders such as acquired hemophilia and congenital FVII deficiency.

1.2 Background Information on LR769

LR769 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 Tissue Factor (TF) can activate factor X to factor Xa directly bypassing FIX or FVIII. Activation of factor X to factor Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin and then converts fibrinogen to fibrin.

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 (GLA-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 (LC) of 152 AA and a C-terminal Heavy Chain (HC) of 254 AA held together by a single disulfide bridge (Cys135-Cys262).

The clinical development plan has been designed to support registration of LR769 for the on-demand treatment of bleeding episodes and for the prevention of excessive bleeding and achievement 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).

This study, PERSEPT 3, will evaluate LR769 for the prevention of excessive bleeding and achievement of hemostasis in congenital hemophilia A or B patients who have inhibitors (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); are aged 6 months to 75 years, inclusive; and who are undergoing elective surgical or other invasive procedures. Administration of LR769 will be performed just prior to surgery/procedure and will be repeated during and after the surgery/procedure to achieve and maintain adequate hemostasis as determined by the investigator's judgment.

Interim efficacy and safety results from a study (RB-FVIIa-006-13, PERSEPT 1) in patients 12 years and older provide the basis for the current study. The available results of this study and of the Phase 1b study completed earlier are more extensively described in the current LR769 Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To assess the efficacy of LR769 to prevent excessive bleeding and achieve hemostasis in hemophilia A or B patients with inhibitors to FVIII or FIX undergoing elective surgical or other invasive procedures.

2.2 Secondary Objective

The secondary objective of this study is:

- To assess the safety of LR769 including the immunogenic potential of the drug product.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an international, multicenter, single-arm, Phase 3 study. Patients aged 6 months to 75 years, inclusive, who have congenital hemophilia A or B with inhibitors and who are scheduled for an elective surgical or other invasive procedure will be enrolled. Different age restrictions may apply per local regulation and ethical considerations; enrollment of children <12 years of age will not begin until after review of data from the PERSEPT 2 study by the DMC.

After obtaining Informed Consent from the patient and/or the patient's parent(s)/legal guardian(s), patients who are scheduled for an elective surgical or other invasive procedure will undergo screening assessments to determine eligibility.

Patients who are or were participating in another LR769 study (eg, PERSEPT 2) and who meet all eligibility criteria will be allowed in this study if the study is open for enrollment in that age group.

Safety follow up will continue until 28 (±3) days after the last dose of LR769.

Initial Treatment: For a minor elective surgery or other minor invasive procedure, a dose of 75 µg/kg of LR769 administered within ≤2 minutes will be used as the initial dose; for a major elective surgery or other major invasive procedure, a dose of 200 µg/kg of LR769 administered within ≤2 minutes will be used as the initial dose before the surgical incision or start of the invasive procedure. For both minor and major procedures, administration will be repeated no more frequently than every 2 hours (±5 minutes) at a dose of 75 µg/kg during and after surgery or invasive procedure.

Treatment for Major Surgical Procedures: The initial dose (200 µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours after completion of procedure. The minimum duration of LR769 treatment for major procedures will be 5 days, according to the frequency listed in Table 1. The patient will be followed postoperatively according to the site's standard of care.

Discharge and Follow up: If the patient requires further treatment with LR769 after hospital discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines specified in Table 1. The efficacy assessment will be completed by the investigator or designee every 24 (±2) hours and at last administration of LR769 via telephone. The assessment 48 (±4) hours after the last dose of LR769 will be performed by the investigator at the study center. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769 administration.

If physical therapy is planned, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended each time before physical therapy begins. Similarly, before drain

or suture removal, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended.

Treatment for Minor Surgical or Invasive Procedures: The initial dose (75µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours, although, depending on the investigator's judgment, the interval may be extended in the first 48 hours. The minimum duration of LR769 infusion for minor procedures will be 2 days, according to the frequency listed in Table 2. For less invasive procedures, such as peripherally inserted central catheter (PICC) or Port-a-Cath placement and for procedures such as dental extractions, the patient may be treated for ≤48 hours if the investigator determines this shorter duration of treatment is sufficient to achieve hemostasis.

Discharge and Follow up: If the patient requires further treatment with LR769 after the outpatient procedure or hospital discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines in Table 2; however, the efficacy assessment will be completed by the investigator or designee every 24 (±2) hours from completion of the procedure and at last administration of LR769 via telephone, and by the investigator at 48 (±4) hours after the last dose of LR769 at the study center. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769 administration.

Efficacy Assessments: Immediately after completion of the procedure, the surgeon/practitioner will assess the intraoperative efficacy of LR769. The patient's intraoperative response to treatment with LR769 will be assessed by the surgeon/practitioner and recorded as "excellent," "good," "moderate," or "poor." Subsequent assessments will be performed by the investigator or designee at all other timepoints. The final assessment (which represents the primary efficacy outcome) will be performed by the investigator at the study center 48 (±4) hours after last dose of LR769 and will be based upon the totality of assessments performed on the patient at each timepoint.

Patients will be assessed for safety throughout the study until 28 (±3) days after the last dose of LR769 via physical examinations, clinical safety laboratory tests, assessments for thromboembolic events and postoperative assessments, vital signs, immunogenicity tests, and the recording of adverse events (AEs). The Schedule of Events is presented in Appendix 1.

3.2 Rationale for Study Design and Control Group

At this time, there are no European Medicines Agency (EMA) or United States (US) 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). This guideline 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 preparing LFB USA's clinical development plan (including studies in the pediatric population). Indeed, the epidemiology of patients with hemophilia with inhibitors to

FVIII and FIX is similar to that of all patients with hemophilia B. This study is the third in a series of three for full development of LR769.

This is a single-arm, non-comparative study, ie, not an active or placebo-controlled 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®), plasma-derived FVIIa (pdFVIIa) or NovoSeven®. Such studies would need to be designed as a non-inferiority study, and the most obvious comparator would be NovoSeven® 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.

3.3 Study Duration and Dates

The study will continue until at least 12 surgical procedures (including a minimum of 6 major surgeries, of which at least 5 must be procedures other than central venous access device placement) have been performed in at least 6 patients.

The duration of the patient's participation in the study (from signing the Informed Consent form until the last follow-up visit) may vary. In patients undergoing a major procedure the duration of participation will be approximately 6 to 9 weeks (or longer if treatment with LR769 is extended). In patients undergoing a minor procedure the duration of participation will be approximately 5 to 8 weeks (or longer if treatment with LR769 is extended).

4 STUDY POPULATION SELECTION

4.1 Study Population

The population for this study is patients, aged 6 months to 75 years, inclusive, who have congenital hemophilia A or B complicated by high titer inhibitors (peak BU ≥5). Some patients may have low levels of inhibitors i.e, BU<5 but still cannot be treated with FVIII or FIX concentrates since they are known to have a strong memory (anamnestic) response after re-exposure to factor concentrates. This should be evident from the patient records where it is documented that administration of Factor VIII or IX has led to a sharp increase in inhibitor levels (BU>5), preventing further use of the factor concentrate (ie, need for bypassing agent). A small group of patients may, despite titers of inhibitors <5 BU, be refractory or intolerant to increased dosing with factor concentrates. This may be the case when there is an allergic response to factor concentrates (with Factor IX). Refractory patients may fail to exhibit a documented anamnestic response due to variability in the Bethesda inhibitor assay or due to diminished titers after long periods without exposure to factor concentrate. It would not be considered ethical to expose such patients to factor when their medical history indicates a high likelihood of a rapid and/or significant increase in their inhibitor titers. The allergic response or ineffective treatment with factor concentrates despite low inhibitor titer (BU<5) should be evident from the patient records with detailed description of the insufficient effect of Factor VIII or IX concentrate, thus confirming the need for a bypassing agent. 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 if they are scheduled for an elective surgical or other invasive procedure. Details for these potential anamnestic or refractory patients will be obtained for patients lacking an inhibitor titer of ≥5 BU to document the high-responding features of their inhibitors (including documentation through their medical history of pre- and post-factor infusion levels of Factor VIII or IX, and the corresponding BU titer levels).

Different age restrictions may apply per local regulation and ethical considerations; enrollment of children <12 years of age will not begin until after review of data from the PERSEPT 2 study by the DMC.

Patients who are or were participating in another LR769 study (eg, PERSEPT 2) are allowed in this study, if the study is open for enrollment in that age group.

Both major and minor surgical or other invasive procedures are allowed in the study.

Major Surgical Procedures: Major surgical procedures are those that usually require ≥5 days of factor replacement in hemophilia patients with inhibitors and typically involve entry into a body cavity and/or organ removal or similarly complex procedures. These include, but are not limited to, the following: abdominal (e.g., cholecystectomy, bowel resection, appendectomy), thoracic (e.g., lobectomy, mediastinal procedures), orthopedic (eg, spinal, hip and knee surgery, joint replacements, synovectomy), genitourinary (eg, prostate resection, non-endoscopic bladder surgery), neurological, and cosmetic/reconstructive surgery (eg, facelift, burn scar surgery).

Placement of a central venous access device may qualify as a major surgical procedure if the complexity of the procedure and patient require ≥ 5 days of coagulation factor replacement.

Minor Surgical Procedures: Minor surgical or other invasive procedures typically require <5 days of factor replacement and usually involve the skin, mucous membranes, or superficial connective tissue and include, but are not limited to, the following: placement of a PICC or other central venous access device, isotopic synovectomies, tooth extractions, and skin biopsies. Patients who are about to undergo invasive procedures, including lumbar puncture, arterial blood gas determination, bronchoscopy with brushings or biopsy, and gastrointestinal endoscopy with biopsy are allowed in the study as well; these are also regarded as minor procedures.

4.2 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. a positive inhibitor test BU ≥5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally), OR
   b. an inhibitor test BU <5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally) but expected to have an anamnestic response to FVIII or FIX, as demonstrated by a history of a high-responding inhibitor manifested by a previous anamnestic response, defined as a peak inhibitor titer > 5 BU after re-exposure to factor concentrates, precluding the use of FVIII or FIX products to treat or prevent bleeding, OR
   c. an inhibitor test BU <5 (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected centrally) but expected to be refractory to FVIII or FIX, as demonstrated by the patient's history of previous failure to respond to FVIII or FIX concentrates, even in the absence of a documented anamnestic response, precluding the use of FVIII or FIX products to treat or prevent bleeding episodes.
3. be ≥6 months to ≤75 years of age; different age restrictions may apply per local regulation and ethical considerations (enrollment of children <12 years of age will not begin until after review of data from the PERSEPT 2 study by the DMC)
4. be scheduled for an elective surgical or other invasive procedure
5. be capable of understanding and willing to comply with the conditions of the protocol OR in the case of a patient <18 years of age, parent(s)/legal guardian(s) must be capable of understanding and willing to comply with the conditions of the protocol
6. have read, understood, and provided written Informed Consent (patient and/or parent(s)/legal guardian(s) if the patient is <18 years of age) or Assent, if applicable

4.3 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 (ie, the patient should not be receiving systemic immunosuppressive medication; CD4 counts at screening should be >200/µl)
3. known intolerance to LR769 or any of its excipients
4. currently receiving ITI therapy
5. have a known allergy or hypersensitivity to rabbits
6. have platelet count <100,000/µL
7. have received an investigational drug within 30 days of the planned first LR769 administration, or is expected to receive such drug during participation in this study (with the exception of patients who are or were participating in another LR769 study, eg, a study assessing the treatment of bleeding episodes with LR769)
8. have a clinically relevant hepatic (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] >3 times the ULN and/or renal impairment (creatinine >2 times the ULN)
9. 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 LR769, uncontrolled arrhythmia, or current New York Heart Association (NYHA) functional classification score of stages II – IV
10. have an active malignancy (those with non-melanoma skin cancer are allowed)
11. 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 trial participation or trial outcome (eg, a history of non-responsiveness to bypassing products)
12. be using 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 LR769
13. have active gastric or duodenal ulcer disease

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

5.1.1 Study Drug

Coagulation Factor VIIa (Recombinant), LR769, is a pure FVIIa product produced using recombinant technology. It will be provided in a vial as a lyophilized powder to be reconstituted with water for injection.

5.1.2 Placebo

Not applicable.

5.2 Treatments Administered

5.2.1 Selection and Timing of Dose for Each Patient

The treatment regimen used in this study is selected based on a Phase 1b study assessing the pharmacokinetic (PK) and pharmacodynamic (PD) effects of 3 doses of LR769 (25, 75, 225 µg/kg) in hemophilia A or B patients, as well as from a Phase 3 study which confirmed the clinical efficacy of 75 and 225 µg/kg LR769 for the treatment of bleeding episodes predicted based upon the PK/PD correlation in the Phase Ib trial. Based upon the demonstrated PK/PD relationship as well as the efficacy noted for achieving hemostasis in mild/moderate bleeding episodes, the initial dosing will employ 75 µg/kg prior a minor surgical procedure. However, to account for the more extensive tissue damage in major surgical procedures and resulting greater hemostatic challenge, a dose of 200 µg/kg before a major surgical procedure will be used. These doses are expected to provide a PD effect that will be sufficient to effectively prevent excessive bleeding during and after surgical/invasive procedures and achieve and maintain hemostasis. Additional doses for the post-procedure setting are outlined in detail in Sections 5.2.2 and 5.2.3 below.

Preliminary efficacy and safety results of a study (RB-FVIIa-006-13, PERSEPT 1) in patients 12 years and older provide evidence that on-demand LR769 doses of 75 µg/kg every 2-3 hours effectively control bleeding episodes in hemophilia A or B patients with inhibitors. The available results of this study and of the Phase 1b study completed earlier are more extensively described in the current LR769 Investigator's Brochure.

5.2.2 Treatment for Major Surgical Procedures

The initial dose of LR769 (200 µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours after completion of the procedure. The minimum duration of LR769 treatment for major procedures will be 5 days, according to the frequency listed in the table below.

Table 1. Dose(s) and Dosing Schedule(s) for Major Surgical Procedures

Day	Dose	Recommended Frequency
Day 0 (within 2 minutes of surgical incision or invasive procedure)	200 µg/kg	Initial dose
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes)
Days 3- 4	75 µg/kg	Intervals of up to every 4 hours but not more frequently than every 2 hours
Days 5-6	75 µg/kg	Intervals of up to every 6 hours but not more frequently than every 2 hours
Days 7-10	75 µg/kg	Intervals of up to every 8 hours but not more frequently than every 2 hours
Day 11 to Last Administration of LR769	75 µg/kg	Intervals of up to every 12 hours but not more frequently than every 2 hours

NOTE: If clinically indicated because of oozing or similar findings suggesting the need for more frequent LR769 infusions, the treatment interval may be shortened in consecutive doses within the guidelines stated in Table 1.

If the patient requires further treatment with LR769 after hospital discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines specified in Table 1. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769 administration.

If physical therapy is planned, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended each time before the therapy begins. Similarly, before drain or suture removal, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended.

5.2.3 Treatment for Minor Surgical or Other Invasive Procedures

The initial dose of LR769 (75 µg/kg) will be followed by repeated administration of 75 µg/kg of LR769 every 2 hours (±5 minutes) for the first 48 hours**.** The minimum duration

of LR769 infusion for minor procedures will be 2 days, according to the frequency listed in the table below.

Table 2. Dose(s) and Dosing Schedule(s) for Minor Surgical or Other Invasive Procedures

Day	Dose	Recommended Frequency
Day 0 (within 2 minutes of surgical incision or invasive procedure)	75µg/kg	Initial dose
Day 0 (post first dose) – 48 hours	75 µg/kg	Every 2 hours (±5 minutes) initially. Interval may be increased upon the investigator's judgment
Day 3 to Last Administration of LR769	75 µg/kg	Intervals of up to every 24 hours but not more frequently than every 2 hours

*For less invasive procedures, such as PICC or Port-a-Cath placement and for procedures such as dental extractions, the patient may be treated for ≤48 hours if the investigator or designee determines this shorter duration of treatment is sufficient to achieve hemostasis.

NOTE: If clinically indicated because of oozing or similar findings suggesting the need for more frequent LR769 infusions, the treatment interval may be shortened in consecutive doses within the guidelines stated in Table 2.

5.2.4 All Procedures

If the patient requires further treatment with LR769 after discharge, the patient will administer LR769 at home according to the investigator's judgment and the dosing guidelines in Sections 5.2.2 and 5.2.3. The patient will be provided with LR769 and directions for its storage, reconstitution and administration along with a patient diary in which to record LR769 administration.

5.3 Method of Assigning Patients to Treatment Groups

The method of assigning patients to treatment groups is not applicable as this is a study with a single treatment group.

5.4 Blinding

Not applicable.

5.5 Concomitant Therapy

All concomitant therapies, including the use of blood products such as red blood cells, platelets, fresh frozen plasma, fibrinogen, etc, will be recorded in the patients' medical records and/or patients' diaries and in the eCRF. Concomitant therapies, including date, time, and dose, will be recorded from 30 days prior to screening and throughout the study until the end of the follow-up period.

5.6 Restrictions

5.6.1 Prohibited Medications

All aspirin, NSAIDs, herbs, natural medications, or any other drug with platelet inhibitory properties must be discontinued at least 1 week prior to elective surgical or other invasive procedure and for the duration of treatment with LR769.

Additional restrictions to concomitant therapies include the use of other sources of FVIIa, such as aPCC (FEIBA®) or NovoSeven®. These products may be used only if the response to LR769 is considered insufficient (ie, treatment failure), in which case these bypassing agents may be used for rescue therapy.

Other agents for the prevention of excessive bleeding during surgical or other invasive procedures, such as antifibrinolytics, are allowed and will be recorded on the eCRF.

5.6.2 Prior Therapy

At least 24 hours must have passed between the last administration of a FVIIa-containing product (aPCC (FEIBA®) or (NovoSeven®) and the first LR769 administration.

5.6.3 Prior Gastrointestinal Distress/Ulcers

Patients with active gastric or duodenal ulcer disease are not allowed to participate in this study, in accordance with Exclusion Criterion 13.

5.6.4 Fluid and Food Intake

No restrictions on fluid or food intake apply.

5.6.5 Patient Activity Restrictions

Patients should not undergo physical therapy before the fourth day post-surgical or invasive procedure. If physical therapy is planned, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended each time before the therapy begins. Similarly, before drain or suture removal, an IV bolus dose of 75 µg/kg of LR769 administered within ≤2 minutes is recommended.

5.7 Treatment Compliance

All patients will be treated with LR769 in the hospital or outpatient treatment center prior to, during, and immediately after the surgical or other invasive procedure. Patients may be discharged from the hospital or outpatient treatment center and treated at home at the investigator's discretion. During the patient's hospitalization for the procedure, compliance is managed by the site staff. If the patient continues treatment with LR769 after discharge from the hospital or outpatient treatment center, he will be given a patient diary in which to record the exact dose and time of LR769 administration.

5.8 Packaging and Labeling

LR769 will be supplied in clear glass vials as lyophilized powder in 1 mg and 5 mg. The vials will be labeled using multilingual labels which will comply with local regulations and requirements. Vials will be packed in an outer box. In addition, prefilled syringes with water for injection for reconstitution as well as supplies for reconstitution and administration of LR769 will be provided. Study staff will refer to a separate Pharmacy Manual that will describe the appropriate directions, and patients will refer to "Instructions for Use." if discharged home while still on treatment.

5.9 Storage and Accountability

LR769 must be stored in a safe and secure place at the study center or at home. LR769 is to be stored at 36° to 86° F (2-30°C), is not to be frozen, and must be protected from light. The investigator is fully responsible for LR769 stored at the study center. Access at the study center will be strictly limited to the investigator and designated staff. Neither the investigator nor designated staff may provide LR769 to any patient not in the study. Dispensing of LR769 may be delegated, e.g., to a hospital pharmacy, as locally applicable. Patients who are given LR769 for home administration will be instructed to return the used and any unused vials to the site.

All LR769 received at the investigational site will be documented on LR769 drug accountability forms. This documentation must be available for review by the monitor at the monitoring visit to confirm proper LR769 management.

5.10 Investigational Product Retention at Study Site

All used and unused vials of LR769 will be retained until drug accountability has been performed by the monitor. For this purpose, the investigator or designated staff will keep all used vials, including those returned by patients who administered LR769 at home, for the accountability check by the monitor (unless local regulation does not allow this).

All unused vials will be returned or destroyed according to the instructions of the Sponsor at the end of the study. A separate pharmacy manual will be prepared that will describe the appropriate procedures.

6 STUDY PROCEDURES

6.1 Informed Consent

All patients will be informed of the aims of study, the possible AEs, the procedures and possible risks to which they will be exposed, and how treatment and dose will be determined. They will be informed as to the strict confidentiality of their personal data, and that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician. It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he wants. Once the patient completely understands the study and its procedures and risks, he will be asked to sign and date the Informed Consent. Study procedures may not begin until after the Informed Consent is signed and dated.

If the patient is younger than 18 years of age, his parent(s)/legal guardian(s) will receive the same information. His parent(s)/legal guardian(s) will sign and date the Informed Consent.

The patient may, depending on his age, receive age-appropriate information as well as be asked to sign and date an Assent form. Age of providing information and Assent form may differ among institutions and will be determined by local law and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

Once the Informed Consent and/or Assent has been signed and dated by the patient and/or parent(s)/legal guardian(s), the patient is considered enrolled in the study.

6.2 Medical History

The medical history of each patient will be obtained. Specific information will be recorded in the source records and on the eCRF relating to any prior or existing medical conditions/surgical procedures involving the following: infectious diseases (including viral infections, such as hepatitis and human immunodeficiency virus [HIV]), allergies including allergic responses to LR769 and its excipients (arginine HCl, isoleucine, trisodium citrate dihydrate, glycine, lysine HCl, polysorbate 80), metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, head/ears/eyes/nose/throat (HEENT), breasts, respiratory, cardiovascular, gastrointestinal/hepatic, genitourinary/renal, neurologic, and psychiatric/psychosocial.

In addition, specific detailed information regarding the clinical symptoms and treatment of the hemophilia and patient bleeding history will be collected. This will include the following: type of hemophilia (A or B), history of bleeding episodes, severity (mild, moderate or severe), inhibitor level, date of first detection of inhibitors, concomitant medication use, and response to FVIII or FIX if applicable in case of either anamnestic or refractory response to factor administration.

Demographics (date of birth, race/ethnicity, and sex) will also be collected.

6.3 Physical Examination

6.3.1 All findings from physical examinations will be recorded on source documents and entered into the eCRF. The standard physical examination will include the following observations / measurements: height, weight, general appearance, skin, HEENT, lymph nodes, heart, lungs, abdomen, extremities/joints, neurological, and mental status. Postoperative Assessments

The patient will be followed postoperatively according to the site's standard of care. Postoperative assessments include assessing patient's incision or procedure site for inflammation, bleeding, infection, oozing, and discoloration.

6.4 Vital Signs

Vital signs will include systolic and diastolic blood pressures (mmHg), heart rate (beats/minute), respiratory rate (breaths/minute), and body temperature (°C or °F, sublingual or tympanic).

6.5 Electrocardiography

6.5.1 12-Lead Electrocardiograms

A standard 12-lead electrocardiogram (ECG) will be performed in supine position at Screening, and will be reviewed for any clinically relevant abnormalities by a qualified physician prior to the first administration of LR769.

6.6 Clinical Laboratory Tests

After the sponsor authorizes enrollment of patients <12 years old, the investigator will contact the Medical Monitor regarding any such patient for adaptation of the blood sample schedule to the patient's body weight in consideration of ICH Harmonised Tripartite Guideline "Clinical Investigations of Medicinal Products in the Paediatric Population, ICH Topic E 11," (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002926.pdf).Blood volume drawn cannot exceed 3% of the total blood volume of the patient during a period of 4 weeks and cannot exceed 1% of the total blood volume at any single time.

If the local lab is unable to perform analyses from the recommended volumes, the PSI medical monitor or lab specialist should be contacted in order to discuss possible volumes. In such cases blood volumes will be calculated individually, taking into account patient's weight and applicable requirements in order not to exceed 1% at any single time and 3% within 4 weeks.

Table 3 includes estimates for the amount of blood to be drawn for pediatric patients who weigh <12 kg.

Table 3. Total Amounts (mL) of Blood Taken During the Study for Patients <12 kg

	Screen[a]	Pre Surgery	24 hrs post procedure	7-14 days post first dose	48 hrs post last dose	28 days post last dose/EOS
Hematology	1		1		1	1
PT and aPTT (local lab)	3					
Chemistry	2		2		2	2
Factors VIII or IX, and Inhibitors (central lab only)	2.8					
Immunogenicity and serum storage sample		2				3
Immunogenicity				1.2	1.2	
Totals	8.8	2	3	1.2	4.2	6

EOS = end of study

[a] Screening visit will be spilt into 2 different days if the total volume of blood drawn is to exceed 0.8 mL/kg at a single time.

Serology not performed for pediatric patients < 12 kg.

Table 4 includes estimates for the amount of blood to be drawn for pediatric patients who weigh ≥12 kg and <27 kg.

Table 4. Total Amounts (mL) of Blood Taken During the Study for Pediatric Patients ≥12 kg and <27 kg

	Screen[a]	Pre Surgery	24 hrs post procedure	7-14 days post first dose	48 hrs post last dose	28 days post last dose/EOS
Hematology	1		1		1	1
PT and aPTT and Factor VIII or IX and Inhibitors (local lab)	4.5					
Serology	4					
Chemistry	2		2		2	2
Factors VIII or IX and Inhibitors (central lab)	4.2					
Immunogenicity and serum storage sample		3				4
Immunogenicity				2	2	
Totals	15.7	3	3	2	5	7

EOS = end of study

[a] Screening visit will be spilt into 2 different days if the total volume of blood drawn is to exceed 0.8 mL/kg at a single time.

Table 5 includes estimates for the amount of blood to be drawn for pediatric patients who weigh ≥27 kg.

Table 5. Total Amounts (mL) of Blood Taken During the Study for Pediatric Patients ≥27 kg

	Screen	Pre Surgery	24 hrs post procedure	7-14 days post first dose	48 hrs post last dose	28 days post last dose/EOS
Hematology	2		3		3	3
PT and aPTT and Factors VIII and IX and Inhibitors (local lab)	6					
Serology	4					
Chemistry	4		5		5	5
Factors VIII or IX and Inhibitors (central lab)	4.2					
Immunogenicity and serum storage sample		3				4
Immunogenicity				2	2	
Totals	20.2	3	8	2	10	12

EOS = end of study

Table 6includes estimates for the amount of blood to be drawn for adult patients (≥18 years old).

Table 6. Total Amounts (mL) of Blood Taken During the Study for Adult Patients (≥18 Years)

	Screen	Pre surgery	24 hours post procedure	7-14 days post first dose	48 hours post last dose	28 days post last dose/EOS
Hematology	4		4		4	4
PT and aPTT and Factors VIII and IX and Inhibitors (local lab)	8					
Serology	6					
Chemistry	8		8		5	5
Factors VIII or IX and Inhibitors (central lab)	5.7					
Immunogenicity, serum storage sample		5				5
Immunogenicity				3	3	
Totals	31.7	5	12	3	12	14

EOS = end of study

6.6.1 Laboratory Parameters

6.6.1.1 Clinical Safety Laboratory Tests

The clinical safety laboratory tests for patients ≥12 kg are presented in Table 7 and will be carried out by the local laboratory of the site (FVIII or FIX concentration as well as inhibitor testing will also be analyzed at the central laboratory) at Screening. Hematology, chemistry, and urinalysis will be repeated as specified in Appendix 1.

Table 7. List of Laboratory Tests

Hematology:

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

Urinalysis (dipstick):

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

Serology[1]

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

Serum Chemistry:

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

Coagulation[1]:

- FVIII[2] or FIX[3]
- FVIII[2] or FIX[3] inhibitors
- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

Note: laboratory tests may vary depending on the weight of the patient (see Section 6.6).

[1] At Screening only

[2] In hemophilia A patients only

[3] In hemophilia B patients only

6.6.1.2 Factor and Inhibitor Tests

The concentration of factor VIII (in hemophilia A patients) and FIX (in hemophilia B patients) as well as 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. FVIII or FIX and titer of inhibitors to FVIII or FIX tests will be performed at the local and central laboratories, except for patients <12 kg where samples will be only collected for testing at the central laboratory.

6.6.1.3 Immunogenicity Testing

Serum samples to test for antibodies against LR769 and any host-related impurities will be taken as specified in Appendix 1. Testing for antibodies against LR769 will be done by a screening assay (electrochemiluminescent method) that is able to detect all antibody isotypes. If the sample is screen positive (which is expected in about 5% of samples), the sample will be tested in a confirmatory assay using binding inhibition as a way to confirm the specificity of the signal seen in the screening assay. If confirmed positive, the sample will be tested in an assay that has been set up to determine if antibodies in patient plasma that are known to bind LR769 (as suggested by the screening and confirmatory assay) will also *neutralize* FVIIa clotting activity. A dot blot assay has been developed to screen the patient samples for reactivity to rabbit's milk proteins. This will allow identification of patients who are generating an immune response to milk proteins as a result of LR769 treatment.

6.6.1.4 Storage Samples

Serum samples will be taken and stored (for a maximum of 5 years after the end of the study) for purposes of any safety evaluations deemed necessary in the future (eg, infectious disease evaluations). These samples will be stored by the Sponsor (or designee) in a central location.

6.6.2 Sample Collection, Storage, and Shipping

A separate laboratory manual will be prepared that will describe the appropriate sample collection, storage, and shipping procedures.

6.7 Dispensing Study Drug

When treatment is taking place in the hospital prior to, during, and after surgery, LR769 will be dispensed to the study staff or patient according to the local procedure of the study center. If the patient has been discharged home, he will be provided with LR769 and directions for its storage, reconstitution and administration.

6.8 Efficacy Assessments

Efficacy Assessments:
The intraoperative efficacy of LR769 will be assessed by the surgeon/practitioner; all other efficacy assessments will be made by the investigator or designee as specified in Appendix 1. Assessments for major and minor procedures will be performed at the same timepoints.

The final assessment (which represents the primary efficacy outcome) will be performed by the investigator at the study center 48 (±4) hours after the last dose of LR769 and will be based upon the totality of the assessments performed on the patient at each timepoint, also taking into consideration the number of (interventions for) bleeding episodes, oozing, blood transfusions, and the total amount of LR769 used.

All efficacy assessments will be recorded in the patient's source records and on the eCRF.

Intraoperative Assessment of Efficacy by Surgeon/Practitioner

The surgeon/practitioner's rating of intraoperative efficacy of LR769 will be based on the following parameters:

- Estimated blood loss in the surgical patient as compared to the maximum expected volume of blood loss in a patient without a bleeding disorder:
  - Prior to surgery, the surgeon will note if the procedure is major or minor and the type of anesthesia that is planned, and estimate the maximum expected volume of blood loss based upon the type of surgery and the surgeon/practitioner's previous experience in a patient who does not have a bleeding disorder. After the procedure, the surgeon/practitioner will determine the actual characteristics of the procedure and estimate the volume of blood lost during the procedure using the following factors as a guide: volume of drainage fluid, volume of fluid on sponges and towels, fluid replacement given, transfusion requirements, etc. The maximum expected volume of blood loss and the estimated volume of blood loss during the procedure will be recorded.
  - The surgeon/practitioner will assess the intraoperative hemostasis by comparing the estimated intraoperative blood loss with the maximum expected blood loss estimated prior to the procedure as well as the amount of fluid replacement given, transfusion requirements, hemodynamic stability, etc

Comments from the surgeon/practitioner may be necessary if extenuating circumstances occurred (eg, an artery was briefly severed and required additional time for surgical control of the bleeding creating a larger than expected blood loss.

Taking into account the above parameters, the intraoperative response to treatment will be rated as follows:

- Excellent: intraoperative blood loss similar to or less than expected for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no blood component transfusion is required
- Good: intraoperative blood loss that is greater than expected (but not more than 50% greater) for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no unexpected increased blood component transfusion requirement
- Moderate: intraoperative blood loss that is substantially greater than expected (more than 50% greater) for this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; additional blood component (within 2-fold greater than expected) transfusion is necessary
- Poor: uncontrolled intraoperative blood loss, not explained by a surgical/medical issue other than hemophilia, that requires intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or leads to hypotension or unexpected transfer to Intensive Care Unit [ICU])

Investigator or Designee Assessment of Hemostasis on Postoperative Days

- Excellent: postoperative blood loss similar to or less than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure; no blood component transfusion is required
- Good: postoperative blood loss greater than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; no unexpected need for blood component transfusion
- Moderate: postoperative blood loss that is substantially greater than expected following this type of procedure in a patient who does not have a bleeding disorder and who is undergoing the same surgical or other invasive procedure, not explained by a surgical/medical issue other than hemophilia; additional blood component [within 2-fold greater than expected] transfusion is necessary
- Poor: uncontrolled postoperative blood loss, not explained by a surgical/medical issue other than hemophilia that requires intervention (rescue therapy requirement [bypass agent or porcine FVIII], and/or increased blood component [>2-fold greater than expected] transfusion, and/or leads to hypotension or unexpected transfer to Intensive Care Unit [ICU])

6.8.1 Efficacy Endpoints

Primary efficacy endpoint:

- Percentage of surgical or other invasive procedures with a "good" or "excellent" response to LR769 treatment 48 (±4) hours after the last administration of LR769 as assessed by the investigator

Secondary efficacy endpoints:

- Percentages of success as defined as the combination of "good" and "excellent" responses by the investigator or designee for all efficacy timepoints other than the primary
- Percentages of "poor," "moderate," "good," and "excellent" response by the investigator or designee for all efficacy timepoints
- Percentages of success as defined as the combination of "good" and "excellent" responses by the surgeon/practitioner
- Percentages of "poor," "moderate," "good," and "excellent" response by the surgeon/practitioner for the intraoperative period
- Intraoperative blood loss determined by the surgeon/practitioner as compared to the surgeon/practitioner's maximum predicted blood loss
- Number of events requiring transfusion between start of procedure and 48 (±4) hours after last administration of LR769

- Changes in hemoglobin between start of procedure and 48 (±4) hours after last administration of LR769
- Amount of LR769 used. Total, and separated by use in hospital, at home, or for specific reasons (eg, physical therapy, or other reasons like drain or suture removal)
- Number and type of bleeding episodes at the surgical site between start of procedure and 48 (±4) hours after last administration of LR769
- Number of surgical interventions/re-explorations for bleeding episodes between start of procedure and 48 (±4) hours after last administration of LR769

6.9 Adverse Events Assessments

6.9.1 Performing Adverse Events Assessments

An AE is defined as any undesirable physical, psychological, or behavioral effect experienced by a patient or subject during their participation in an investigational study, in conjunction with the use of a drug or biologic, whether or not product related. Events that match this description but occur between the time of Informed Consent and the first administration of LR769 are also regarded as AEs, but will be listed as *non*-TEAEs. Disease signs, symptoms, and/or laboratory abnormalities already existing prior to Informed Consent are not considered AEs, unless they recur after the patient has recovered from the pre-existing condition or they represent an exacerbation in severity, duration, or frequency.

All AEs will be recorded in the patient's source record and on the eCRFs. A description of the event (preferably medical diagnosis, or if no diagnosis is made, symptom or sign) including start date/time, resolution date/time, seriousness, severity, relationship to LR769, action taken, and outcome will be provided.

All AEs will be followed up until resolution or 30 days after the last dose or early termination, whichever comes first.

6.9.2 Timing

Adverse events will be collected from the time of the signing of the Informed Consent/Assent until resolution or 30 days after the last dose or early termination, whichever comes first. At each specified timepoint, the patient (or parent/legal guardian) will be asked to report any and all AEs experienced since the previous assessment or visit. Specifically, the patient (or parent(s)/legal guardian(s) if the patient is a child), will be asked if the patient experienced any signs and symptoms that may indicate a thromboembolic event occurred. These may include, among others, headache, shortness of breath, chest pain, cyanosis, calf pain, swelling/edema, or redness.

If an AE occurs in PERSEPT 3 and the patient is still enrolled in PERSEPT 2, the AE should only be collected in PERSEPT 3. If the AE is ongoing at the time of rejoining PERSEPT 2, that AE should be only collected in PERSEPT 2 under medical history. If when rejoining PERSEPT

2, there is an exacerbation or recurrence of the AE, this AE should be collected as a new AE in PERSEPT 2.

6.9.3 Severity

Adverse events will be graded by the investigator according to severity:

- 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 relief of symptom(s).
- Moderate: Symptom(s) of a sufficient severity to make the patient uncomfortable. Performance of daily activities is influenced. 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 even life threatening. Severity may cause cessation of treatment with LR769. Treatment for symptom(s) is given. The AE produces sequelae, which may also require (prolonged) treatment.

Note: Severe is not equivalent to serious.

6.9.4 Relationship

For all AEs, the investigator will be asked to record the drug relatedness of the event in the source documents and enter the data in the eCRF. For this assessment the investigator will need to take into account the time relationship between LR769 administration and the occurrence of the event, the expected pharmacology of LR769, the potential contribution of the underlying disease under investigation and/or any other concomitant diseases/medical history, evolution of the event when LR769 was withdrawn, and whether the event recurred after a re-challenge.

The relationship criteria include:

- *Unrelated* (event with a time to drug intake that makes a relationship unlikely and disease or other drugs provide a clear explanation; negative re-challenge)
- *Remote/unlikely* (event with a time to drug that makes a relationship improbable [but not impossible] and disease or other drugs provide plausible explanations)
- *Possibly* (event with reasonable time relationship to drug intake that could also be explained by disease or other drugs and information on drug withdrawal/re-challenge lacking or unclear)
- *Probably* (event occurred within reasonable time relationship to drug intake, is unlikely to be attributed to disease or other drugs and response to withdrawal)
- *Definitely* (event with plausible time relationship to drug intake which cannot be explained by disease or other drugs and/or plausible response to withdrawal and/or definitively pharmacologically plausible and/or positive re-challenge)

6.9.5 Expectedness

An AE is expected if the nature, severity, and outcome of the event are consistent with the reference safety information, ie, the Investigator's Brochure.

6.9.6 Clinical Significance

Clinical significance is defined as any variation in physical/laboratory findings or AE that has medical consequences that result in an alteration in the patient's medical care.

6.9.7 Clinical Laboratory Adverse Events

Any change in laboratory value outside the normal range will be regarded as an AE if the investigator assesses the value as clinically significant. Changes in coagulation parameters expected in hemophilia patients are not regarded as AEs, unless they lead to clinical measures to prevent or treat any untoward events associated with this deviation of the parameter.

6.9.8 Serious Adverse Events

6.9.8.1 Definition

A serious adverse event (SAE) is defined by federal and international regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE.

6.9.8.2 Reporting Serious Adverse Events

The necessity and time requirements for reporting SAEs to the Sponsor or designee and regulatory agencies are as follows:

- All SAEs will be reported via the eCRF system within 24 hours of the investigator's first knowledge of the event, even if the event does not appear to be related to LR769. In case reporting via the eCRF is not available, the SAE may be reported via fax in order to meet the reporting requirements.

In case of failure of the eCRF reporting, SAE forms are to be directed to:

Fax: +1 877-329-8717 (country specific fax instructions will be provided where applicable)

- For all SAEs, a detailed written description that includes anonymized copies of available relevant patient records, autopsy reports, and other documents will be sent within 24 hours of the investigator's first knowledge of the SAE.
- SAEs that are life threatening or result in death, and are unexpected and related to LR769 will be reported to regulatory authorities within 7 days of receipt of the event. Any follow up to the initial SAE report will be submitted to regulatory authorities within 8 days of the initial report (ie, 15 days of receipt of the initial report).
- Any SAE that is unexpected and related to LR769, results in hospitalization or prolongs an existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect will be reported to regulatory authorities within 15 days of receipt of the report. Some regulatory authorities may have alternative timelines for submission of suspected unexpected serious adverse reactions. In those cases, specific local requirements for submission of SAE reports will be applied.
- All SAEs will be followed until resolution or stabilization. Follow-up reports for SAEs reported as 7- or 15-day reports will be submitted within the same time frame as the initial report.

Additionally, the IRB and/or Ethics Committee (EC) must be notified in writing of any unexpected, related SAEs or as required by the local IRB/EC. It is the responsibility of the investigator/contract research organization (CRO) to notify the IRB/EC.

If applicable, SAEs will be reported to the appropriate regulatory agencies by the Sponsor or designee. In case the local regulations require notification through the investigator, the Sponsor will facilitate this process.

6.9.9 Treatment-Emergent Adverse Events

All AEs that occur after the first administration of LR769 will be regarded as treatment emergent (TEAE). All AEs occurring from signing the Informed Consent up to the first administration of LR769 will also be collected and will be referred to as non-TEAEs. Adverse events that are present prior to the first administration of LR769 but subsequently worsen will be considered TEAEs.

A potential risk associated with the administration of LR769 is the occurrence of an allergic or anaphylactic type reaction to either the recombinant molecule or any of the potentially present host-related impurities. Specific emphasis will be put on the observation of the patient after initial administration of LR769 to detect the occurrence of any potential allergic reaction. Symptoms of such a reaction may consist of, but are not limited to:

- Skin redness, rash, hives

- Mucosal and/or skin swelling
- Difficulty breathing
- Hypotension
- Headache
- Dizziness
- Nausea

If any one or more of these symptoms occur, the responsible physician at the site will assess the patient and determine whether the symptoms are consistent with an acute allergic reaction and treat the symptoms accordingly.

Although reported to be rare in hemophilia patients, a potential risk associated with the administration of LR769 is an exaggerated PD action, leading to a thromboembolic event. Specific emphasis will be put on the observation of the patient directly after administration of LR769 as well as during the follow-up assessments to detect the occurrence of any thromboembolic events. Events that may occur are myocardial infarction, ischemic cerebrovascular accident, arterial thrombosis (eg, aorta, intestinal), DVT, and PE. In case signs and symptoms of any of these occur in the patients during the study, the responsible physician at the site will need to assess the symptoms and order and review diagnostic procedures (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) is suggested as guidance for determining the need for additional diagnostic tools.

If an acute allergic reaction or a confirmed thrombotic event occurs in association with the administration of the LR769, such event will be reported in the same manner and timelines as a SAE (see Section 6.9.8.2), even when it does not meet the criteria for seriousness as listed in Section 6.9.8.1.

6.10 Surgical or Invasive Procedure Characteristics

The surgeon/practitioner will determine the following predicted surgical or invasive procedure characteristics and record them prior to the procedure:

- major or minor
- maximum expected blood loss in a patient without a bleeding disorder who is undergoing this type of procedure
- type of anesthesia

After the surgery or invasive procedure, the surgeon/practitioner will determine the actual characteristics of the procedure and record them:

- major or minor
- duration of procedure
- estimated blood loss
- factors that may have influenced bleeding independent of hemostasis, eg, surgical complications, difficulties owing to scarring, adhesions, problems with suturing vessels
- actual type of anesthesia
- complications

6.11 Concomitant Medication Assessments

All concomitant medications (including any blood or blood products) and/or concomitant procedures administered or performed during the study will be recorded in the source record and subsequently captured in the eCRF (including date, time, type of medication or product, and dose or amount).

6.11.1 Excluded Medications

As was stated in Exclusion Criterion 12, the use of aspirin, NSAIDs, herbs, natural medications, or other drugs with platelet inhibitory properties are excluded one week prior to surgical procedure and for the duration of treatment with LR769.

6.12 Study Stopping Rules

The study will be stopped (ie, cease enrollment as well as treatment of already enrolled patients) in the following cases:

- A confirmed thrombotic event has been reported in any of the patients treated in the study
- An acute allergic or anaphylactic reaction, or signs and symptoms strongly indicative of such reaction, has occurred in association with the administration of LR769
- A patient develops a neutralizing antibody to LR769

If one of these events occurs, participating sites, competent authorities, as well as all involved ECs/IRBs, will be informed of the (temporary) stop of the study. Investigations into the case(s) will need to be done and the results will then be reported to the competent authorities and ECs/IRBs, together with a recommendation on whether and how to proceed with the study. Only after approval of the competent authorities and ECs/IRBs may the study continue.

In addition, the DMC could make a recommendation for study termination due to concerns over patient safety or issues relating to data monitoring or quality control.

6.13 Removal of Patients from the Trial or Treatment

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

- The investigator believes it is in the best interest of the patient to discontinue the study
- The Sponsor or investigator terminates the study
- The patient withdraws consent or requests to be discontinued from the study
- The patient is non-compliant

In case of early withdrawal of the patient, he will be asked to perform the 48 (±4) hour visit assessment after last administration of LR769, unless he has withdrawn Informed Consent.

The investigator may discontinue a patient from LR769 treatment for any of the following reasons:

- AE or SAE possibly related to LR769 treatment
- A clinically significant change in the patient's condition that does not allow safe administration of LR769
- Per judgment of the investigator, if an adequate hemostatic response is not achieved with LR769, and the bleeding requires continued treatment, the treating physician should stop treatment with LR769 and treat the patient with a rescue therapy, such as another bypassing agent (e.g., FEIBA® or NovoSeven®) and/or other effective hemostatic treatment. The patient remains eligible for treatment with LR769 for a new surgical procedure taking into account the pharmacodynamic half-life of the rescue therapy given.

6.14 Replacement of Patients

Patients who are removed from the study will only be replaced if their removal results in the minimum number of surgical or other invasive procedures/patients needed for the study not being met.

6.15 Other Study Procedures

There are no other study procedures.

6.16 Appropriateness of Measurements

Efficacy assessments are performed according to existing guidelines and published literature (Shapiro and Cooper, 2012; Shapiro, 2014; Shapiro et al., 1998; Giangrande et al., 2009). In this study, response to treatment with LR769 will be assessed intraoperatively by the surgeon/practitioner and postoperatively by the investigator or designee.

7 STUDY ACTIVITIES

All study activities can be found in the Schedule of Events (see Appendix 1).

7.1 Screening (Days -21 to -1)

- Informed consent signature
- Determine eligibility
- Demographics
- Medical history
- Physical examination
- Clinical safety laboratory tests (hematology, coagulation, serology, chemistry, urinalysis), by local laboratory - per weight requirement
- FVIII/FIX and inhibitor testing, by central laboratory (as confirmed at screening by the institutional lab, with the exception being for patients <12 kg where samples will only be collected for testing at the central laboratory)
- Vital signs
- 12-lead ECG
- Assessment of concomitant medication
- Assessment of AEs

7.2 Surgery/Invasive Procedure and LR769 Treatment

7.2.1 Before Surgery/Invasive Procedure

- Confirm eligibility
- Physical examination (excluding height, including weight, which is the weight to be used for calculating dose of LR769) within 24 hours before the procedure
- An IV bolus dose of 75 µg/kg (for a minor surgery or other minor invasive procedure) or 200 µg/kg (for a major surgery or other major invasive procedure) of LR769 administered within ≤2 minutes before the surgical incision or start of the invasive procedure.
- Predicted surgery/invasive procedure characteristics
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature [sublingual or tympanic])
- Assessment of concomitant medications
- Assessment of AEs
- Immunogenicity sample (including storage serum sample for future use)

7.2.2 During Surgery/Invasive Procedure

After the initial IV bolus dose of LR769 during the surgical or other invasive procedure, patients will be given repeated IV bolus doses of 75 µg/kg of LR769 administered over ≤2 minutes at least 2 hours apart.

7.2.3 Surgeon/Practitioner's Assessment

Immediately after completion of the procedure, the surgeon will:

- Determine the actual surgery/invasive procedure characteristics (major or minor, duration of procedure, factors that may have influenced bleeding independent of hemostasis, actual type of anesthesia, and complications)
- Estimate the blood loss
- Assess the intraoperative efficacy of LR769

The patient's intraoperative response to treatment with LR769 will be assessed by the surgeon/practitioner and recorded as "excellent," "good," "moderate," or "poor." Further details regarding the criteria for the surgeon/practitioner's assessment of intraoperative efficacy are provided in Section 6.8. The surgeon/practitioner will also record any AEs and concomitant medications.

7.3 After Surgery/Invasive Procedure

The patient will be followed postoperatively according to the site's standard of care. Treatment with LR769 following completion of the surgery or invasive procedure will be administered according to the specifications in Section 5.2.2 (major surgical procedures) or Section 5.2.3 (minor surgical or other invasive procedures).

7.3.1 24 Hours ± 2 Hours After Completion of Procedure

- Clinical safety laboratory tests (hematology, chemistry, urinalysis), by local laboratory; per weight requirement
- Administration of 75 µg/kg of LR769 according to the administration schedule determined by the investigator
- Postoperative assessment
- Vital signs
- Efficacy assessment by investigator or designee if treatment with LR769 is ongoing; assessment may be made by phone if the patient has been discharged home
- Assessment of concomitant medications
- Assessment of AEs (including thromboembolic assessments)

7.3.2 Every 24 Hours ± 2 Hours After Completion of Procedure

- Efficacy assessment by investigator or designee as long as treatment with LR769 is ongoing); assessment may be made by phone if the patient has been discharged home
- Postoperative assessment
- Assessment of concomitant medications
- Assessment of AEs (including thromboembolic assessments)

7.3.3 7-14 Days After Start of Treatment with LR769

A sample for immunogenicity will be taken 7-14 days after start of treatment. Depending on the timing (length of time since the patient's first dose of LR769), this visit may be combined with another specified visit.

7.4 Last Dose of LR769

- Last administration of LR769 (for end of treatment only)
- Efficacy assessment by investigator or designee
- Assessment of concomitant medications
- Postoperative assessment
- Assessment of AEs (including thromboembolic assessments)

7.5 Early Termination Procedures

- Efficacy assessment by investigator or designee
- Assessment of concomitant medications
- Postoperative assessment
- Vital signs
- Clinical safety laboratory tests (hematology, chemistry, urinalysis) by local laboratory; per weight requirement
- Assessment of AEs (including thromboembolic assessments)
- Immunogenicity sample (including storage serum sample for future use)
- Physical Examination (excluding height)

7.6 Follow-Up Visits

7.6.1 48 Hours ± 4 Hours After the Last Dose of LR769

- Clinical safety laboratory tests (hematology, chemistry, urinalysis), by local laboratory; per weight requirement

- Review of patient diaries and final study drug accountability (including used vials returned by the patient)
- Vital signs
- Efficacy assessment by investigator
- Assessment of concomitant medications
- Postoperative assessment
- Physical examination (excluding height)
- Assessment of AEs (including thromboembolic assessments)
- Immunogenicity sample

7.6.2 28 Days ± 3 Days After the Last Dose of LR769

- Clinical safety laboratory tests (hematology, chemistry, urinalysis), by local laboratory; per weight requirement
- Assessment of concomitant medications
- Assessment of AEs (including thromboembolic assessments)
- Immunogenicity sample (including storage serum sample for future use)

8 QUALITY CONTROL AND ASSURANCE

This study is sponsored by LFB USA Inc. The Sponsor will delegate specific tasks regarding the conduct of this study to a CRO.

Quality Control Procedures as described in LFB USA's Quality System as well as those of the CRO will be applied. A document describing which procedures will be used for which study activities at each stage of the clinical study will be part of the arrangements between the Sponsor and the CRO. This will ensure patient safety and reliability of the data. Monitoring visits to the study sites will be conducted periodically during the study according a study specific monitoring plan to ensure that all aspects of the protocol are being followed. The study site may be audited by LFB USA's Clinical Quality Assurance auditor (or designee). The study sites will receive written notice in advance of any audit.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All data collected in this study will be displayed using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

9.2 Determination of Sample Size

The sample size was determined based on adaptations of international guidelines for coagulation factors in agreement with US and EU authorities.

9.3 Analysis Populations

The Efficacy Population is defined as all patients who receive LR769 treatment, undergo a surgical or invasive procedure, and have at least 1 efficacy assessment.

The Safety Population is defined as all patients who receive at least 1 dose of LR769.

All efficacy analyses will be performed on the Efficacy Population and all safety analyses will be performed on the Safety Population.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics for all patients will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

9.5 Efficacy Endpoints

Efficacy results will be reported as descriptive statistics. Surgeries will be examined overall as well as by major procedures and minor procedures separately.

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of surgical or other invasive procedures with a “good” or “excellent” response to LR769 treatment as assessed by the investigator at the study center 48 (±4) hours after the last administration of LR769; this assessment will be based upon the totality of assessments performed on the patient at each timepoint also taking into consideration the surgeon’s intraoperative hemostatic assessment, the number of (interventions for) bleeding episodes, oozing, blood transfusions, and the amount of LR769 used.

A point estimate of this endpoint will be calculated together with a Clopper-Pearson exact 95% confidence interval.

9.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Percentages of success as defined as the combination of "good" and "excellent" responses by the investigator or designee for all efficacy timepoints other than the primary
- Percentages of "poor," "moderate," "good," and "excellent" response by the investigator or designee for all efficacy timepoints
- Percentages of success as defined as the combination of "good" and "excellent" responses by the surgeon/practitioner
- Percentages of "poor," "moderate," "good," and "excellent" response by the surgeon/practitioner for the intraoperative period
- Intraoperative blood loss determined by the surgeon/practitioner as compared to the surgeon/practitioner's maximum predicted blood loss
- Number of events requiring transfusion between start of procedure and 48 (±4) hours after last administration of LR769
- Changes in hemoglobin between start of procedure and 48 (±4) hours after last administration of LR769
- Amount of LR769 used. Total, and separated by use in hospital, at home, or for specific reasons (eg, physical therapy, or other reasons like drain or suture removal
- Number and type of bleeding episodes at the surgical site between start of procedure and 48 (±4) hours after last administration of LR769
- Number of surgical interventions/re-explorations for bleeding episodes between start of procedure and 48 (±4) hours after last administration of LR769

Point estimates will be computed together with 95% confidence intervals for the proportion of successes, mean difference between intraoperative blood loss and surgeon/practitioner's maximum predicted blood loss, proportion of events requiring transfusion, mean hemoglobin level at each timepoint, mean amount of LR769 used, and mean number of surgical interventions/re-explorations for bleeding episodes. Clopper-Pearson exact confidence intervals will be used for dichotomous endpoints; confidence intervals for continuous variables will be based on the normal approximation.

9.6 Safety Endpoints and Analysis

Safety endpoints include the following:

- Analysis (including relationship to LR769, severity, and outcome) of AEs/SAEs between first LR769 administration and 28 (±3) days after last administration of LR769
- Analysis of treatment-emergent thromboembolic events between start of procedure and 28 (±3) days after last administration of LR769

- Analysis of allergic and anaphylactic reactions between start of procedure and 28 (±3) days after last administration of LR769
- Analysis of treatment-emergent antibodies against LR769 or host-related impurities between start of procedure and 28 (±3) days after last administration of LR769

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA). The number and percentage of patients with any treatment-emergent AEs (TEAEs) and any treatment-emergent serious AEs (SAEs) will be presented for all patients. An AE will be considered treatment related if it has a definite, probable, or possible relationship to the study treatment or if the relationship to the study treatment is missing. AEs will be summarized at the patient level by MedDRA system organ class (SOC) and preferred term (PT) using frequencies and percentages. AEs will also be tabulated at the event level by SOC, PT, and severity and by SOC, PT, and relationship to study treatment.

The number and percentage of patients with any treatment-emergent thromboembolic event and/or allergic and anaphylactic reactions will be presented for all patients.

For vital signs and clinical laboratory test results (continuous parameters), descriptive statistics for the actual value at each timepoint and the change from baseline to each post baseline timepoint will be tabulated. Two-sided paired t-tests will be used to test whether the mean changes from baseline equal 0. Baseline is defined as the last measurement prior to study treatment. Descriptive statistics for immunogenicity data will also be produced for the specified timepoints.

9.7 Interim Analysis

There are no planned interim analyses for this study.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

The Sponsor will contract a CRO to perform specific study related tasks. The division of responsibilities will be documented in mutually agreed documents. Written procedures will be used in order to assure that the study is conducted according to all applicable rules and regulations.

The investigators will ensure that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and any other local regulations and guidelines.

The investigators will review all study-related documents including the protocol and the current version of the Investigator's Brochure. It is obligatory that the Principal Investigator be familiar with the protocol and all sections of the Investigator's Brochure prior to initiation of the study.

10.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

A copy of the protocol, Investigator's Brochure, proposed Informed Consent/Assent Form and any other written patient information must be submitted to the IRB/IEC for written approval. A copy of the written IRB/IEC approval of the protocol and Informed Consent/Assent form must be received by the Sponsor before recruitment of patients into the study and shipment of investigational drug.

The Principal Investigator/CRO must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the Informed Consent/Assent form. The Principal Investigator/CRO will notify the IRB/IEC of deviations from the protocol or SAEs/reportable safety events at the site or reports of such events received from the Sponsor in accordance with local procedures.

The Principal Investigator/CRO will be responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the study.

The Principal Investigator will promptly report to the IRB/IEC all changes in research activity and all unanticipated problems involving risks to human patients and will not make any changes in the research without prior Sponsor and IRB/IEC approval, except where necessary to eliminate immediate hazards to human patients

10.3 Ethical Conduct of the Study

This study will be conducted in compliance with GCP as described in the International Conference on Harmonisation (ICH) document "Guidance for Industry-E6 GCP: Consolidated Guidance" dated April 1996. These practices are consistent with the principles

stated in the Declaration of Helsinki (October 2013 revised version). All other applicable regulations will be adhered to.

10.4 Patient Information and Consent

Written Informed Consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed. Patients or the parent(s)/legal guardian(s) of the patients who meet general entry criteria will be asked to sign the study specific, IRB/IEC approved Informed Consent Form before any study-specific test or procedures are performed. The written Informed Consent will be obtained after the context of the study has been fully explained to the patient or patient's parent(s)/legal guardian(s) in a language that is easily understood by the patient or the parent(s)/legal guardian(s). There must also be adequate opportunity to ask questions and have those questions answered to their satisfaction. Study personnel will explain that even if a patient agrees or the parent(s)/legal guardian(s) agrees to allow a child to participate in the study and signs an Informed Consent Form, the study-specific test or procedures may demonstrate that the patient is not a candidate for the study.

The written Informed Consent will be prepared in the language(s) of the potential study population and will be administered according to national requirements.

The patient may, depending on his age, receive age-appropriate information as well as be asked to sign and date an Assent Form. Age of providing information and Assent Form may differ between institutions and will be determined by local law and IRB or IEC requirements.

10.5 Patient Confidentiality

Patient participation is voluntary and patients or a patient's parent(s)/ legal guardian(s) may refuse to participate or withdraw from the study at any time and for any reason. Patients and/or their parent(s)/legal guardian(s) will be informed that information about them/their child is being entered into a study database and their consent will be obtained and recorded. Patients will be identified only by a patient number and date of birth. They will be informed as to the strict confidentiality of their patient data, and that their medical records may be reviewed for study purposes by authorized individuals other than their treating physician.

10.6 Study Monitoring

Monitoring visits to the study sites will be conducted periodically during the study according 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 which will be reviewed for verification of 100% of data captured in the eCRF. For this study, source documents include but are not limited to the Informed Consent/Assent Form, patient's medical records, patient diaries, laboratory results, reports of SAE's, and drug accountability logs. It is important that the investigator and relevant study personnel are available during monitoring visits and audits and that sufficient time is devoted to the process.

10.7 Case Report Forms and Study Records

Patient data will be collected both electronically and on paper. The investigators must ensure the accuracy and completeness of the recorded data and provide a signature on the appropriate eCRFs. The investigator's signature for specific eCRFs will be documented in compliance with ICH/GCP guidelines. Visual and/or computer data review will be performed to identify possible data discrepancies. Data cleaning will be performed on all data in the eCRF. Queries will be created in the data management system and will be issued for appropriate response

10.8 Data Monitoring Committee

The Data Monitoring Committee (DMC) is responsible for the oversight of patient safety. The DMC will consist of 3 specialists in the care of hemophilia patients. DMC members will be independent of the study and Sponsor. During the course of the trial, the DMC will review immediate serious adverse drug reactions and quarterly review of SAE listings. In addition the DMC will review the data and recommendation from the DMC in the PERSEPT 2 pediatric study to determine whether enrollment of patients <12 years of age is appropriate for this study.

The DMC will make recommendations, as appropriate, for study modification or termination because of concerns over patient safety or issues relating to data monitoring or quality control. This will be submitted in writing to the sponsor's Medical Monitor for consideration and final decision. However, if the DMC at any time determines that a potential serious risk exists to patients in the study, the DMC Chairperson will immediately notify the Sponsor's Medical Monitor per the DMC Charter.

10.9 Protocol Deviations

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

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 or 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 the guideline is "deviations related to entry criteria, conduct of the trial, patient management, or assessment." An analysis of important protocol deviations will be presented in the CSR.

10.10 Criteria for Terminating Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to patient safety and

protection. Investigators and the associated IRB/IEC will be notified in the event of termination.

Possible reasons for study termination include:

- DMC recommendation
- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue development of LR769

10.11 Criteria for Suspending/Terminating a Study Center

The Sponsor reserves the right to terminate enrollment of patients at a study site at any time after study initiation. Reasons for site termination or suspension include, but are not limited to:

- Non-enrollment of patients
- Significantly slower than expected enrollment
- The study site has multiple and/or important protocol deviations without justification or fails to follow corrective actions
- Failure to obtain/maintain IRB/IEC approval
- Failure to obtain written Informed Consent
- Failure to report SAE within 24 hours of knowledge
- Failure to enter data in the eCRF in a timely manner
- Loss of, or unaccounted for LR769 inventory

10.12 Access to Source Documentation

The monitor (or auditors, regulatory inspectors) will check the eCRF form entries against the original source documents. The consent form will include a statement by which the patients allow the monitor/auditor/inspector access to source data (eg, original laboratory reports) which substantiate information in the eCRF. These personnel, bound by professional confidentiality, will not disclose any personal information.

10.13 Data Generation and Analysis

See the Statistical section of this protocol (Section 9).

10.14 Retention of Data

The investigator/institution should maintain the trial documents as specified in ICH E6 GCP Consolidated Guidance and as required by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. If for any reason the investigator withdraws responsibility for maintaining

the trial documents, custody must be transferred to an individual who will assume responsibility. The Sponsor must receive written notification of this custodial change.

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of LR769. These documents will be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor.

10.15 Financial Disclosure

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

10.16 Publication and Disclosure Policy

The study will be listed in the public database on clinical studies *www.clinicaltrials.gov* and *www.clinicaltrialsregister.eu*. A summary report of the study 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.

Appendix 1 Schedule of Events

Evaluation	Screening Days -21 to -1	Procedures + LR769 Treatment						Follow-Up Visits		
		Pre Procedure	Immediately Postoperative	24 (±2) hrs after procedure completion	Every 24 (±2) hrs after procedure completion	7-14 days after 1st dose of LR769[9]	Last Dose of LR769	Early Termination	48 (±4) hrs after last dose	28 (±3) days after last dose
Informed Consent	X									
Inclusion/Exclusion Criteria	X	X								
Demographics and Detailed Medical History	X									
Physical Examination[1]	X	X[8]						X	X	
Safety Lab Tests										
Hematology, chemistry, urinalysis (local lab)	X			X				X	X	X
Coagulation[10], serology[12]	X									
LR769 Administration[2]		X								
Surgical/Invasive Procedure Characteristics[3]		X	X							
Postoperative Assessment[4]				X	X		X	X	X	
Vital Signs[5]	X	X		X				X	X	
12-Lead ECG	X									

Evaluation	Screening Days -21 to -1	Procedures + LR769 Treatment						Follow-Up Visits		
		Pre Procedure	Immediately Postoperative	24 (±2) hrs after procedure completion	Every 24 (±2) hrs after procedure completion	7-14 days after 1st dose of LR769[9]	Last Dose of LR769	Early Termination	48 (±4) hrs after last dose	28 (±3) days after last dose
Efficacy Assessments[6]										
Surgeon's Assessment			X							
Investigator's Assessment				X	X		X	X	X	
Adverse Event Assessment	X	X[10]								
Concomitant Medication	X	X								
Immunogenicity		X[7]				X[9]		X[7]	X	X[7]

[1] Height will be measured at screening only.

[2] Initial dose of 75 µg/kg (minor surgery or other minor invasive procedure) or 200 µg/kg (major surgery or other major invasive procedure) of LR769 will be administered as an IV bolus dose within ≤2 minutes prior to surgical incision or start of the invasive procedure; subsequent doses of 75 µg/kg of LR769 will be administered as an IV bolus dose of LR769 within ≤2 minutes during and after surgical or other invasive procedure; duration of treatment will be dependent on the type of procedure and the patient's status in accordance with Table 1 and Table 2.

[3] Surgical/invasive procedure characteristics: Predicted surgery/invasive procedure characteristics: major or minor, maximum expected blood loss in a patient without hemophilia, type of anesthesia. Actual surgery/invasive procedure characteristics: major or minor, duration, estimated blood loss, factors that may have influenced bleeding independent of hemostasis, actual type of anesthesia, and complications.

[4] Patients will be followed postoperatively according to the site's standard of care.

[5] Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (sublingual or tympanic); if the patient is discharged before the 24 (±2) hour time point vital signs will be taken at that time.

[6] Intraoperative efficacy will be assessed by the surgeon/practitioner immediately after completion of the procedure and recorded; the primary efficacy endpoint will be determined by the investigator at 48 (±4) hours after last dose of LR769; all other efficacy assessments will be determined by the investigator or designee

[7] Including storage serum sample for potential future use (eg, viral serology)

[8] Weight taken within 24 hours prior to surgery or invasive procedure will be used for calculating the dose of LR769

[9] Depending on the timing (length of time since the patient's first dose of LR769), this assessment may be combined with a pre-specified visit

[10] FVIII or FIX and titer of inhibitors to FVIII or FIX will at local and central lab. Only central lab for patients <12 kg.

[11] Patients will be assessed for signs and symptoms of thromboembolic events, such as pulmonary embolism (eg, shortness of breath, chest pain) or deep vein thrombosis (eg, calf pain, swelling/edema, and redness).

[12] Serology not performed for patients <12 kg.

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