

Official Title: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to <12 years old with Inhibitors to Factor VIII or IX: PerSept 2

NCT Number: NCT02448680

Document: Protocol Amendment 4

Date of the Document: 29 June 2016

Clinical Trial Protocol: LFB-FVIIa-007-14

Study Title: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to <12 years old with Inhibitors to Factor VIII or IX: PerSept 2

Study Number: LFB-FVIIa-007-14

Study Phase: Phase 3

Product Name: Coagulation Factor VIIa (Recombinant), LR769

EudraCT #: 2015-000958-38

IND #: 15183

Indication: LR769 is intended to be used for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in patients with congenital hemophilia A or B with inhibitors to coagulation factors VIII (FVIII) or IX (FIX)

Investigators: Multicenter, multinational study

Principal Investigator: [REDACTED]

Sponsor: LFB USA Inc.

Sponsor Contact: [REDACTED]
Sr. Director Clinical Operations
[REDACTED]
[REDACTED]

Sponsor's Legal Representative: [REDACTED]
Sr. Vice President Regulatory Affairs and Pharmacovigilance
[REDACTED]
[REDACTED]
[REDACTED]

Medical Monitor: [REDACTED]
Vice President Clinical Development
[REDACTED]

Original Protocol:	30 April 2015
Amendment 1	04 August 2015 [REDACTED]
Amendment 2	26 August 2015
Amendment 3	09 October 2015
Amendment 4	29 June 2016

Confidentiality Statement

Part or all of the information in this protocol may be unpublished material. Accordingly, this protocol should be treated as confidential information and its use restricted to supplying information to investigators, regulatory authorities, ethics committees, and other personnel involved in this study who need to be aware of the content of the protocol.

TABLE OF CONTENTS

SYNOPSIS.....	7
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS.....	19
1 INTRODUCTION	21
2 STUDY OBJECTIVES.....	24
2.1 Primary Objectives.....	24
2.2 Secondary Objective	24
2.3 Other Objective.....	24
3 INVESTIGATIONAL PLAN.....	25
3.1 Overall Study Design and Plan.....	25
3.1.1 Phase A (Initial Safety and PK Phase).....	27
3.1.2 Phase B (Treatment Phase)	27
3.1.2.1 Classification of Severity of Bleeding Episodes.....	27
3.1.2.2 Treatment of Mild/Moderate Bleeding Episodes.....	28
3.1.2.3 Treatment of Severe Bleeding Episodes	29
3.1.2.4 Rescue Treatment.....	30
3.1.2.5 Prevention of Bleeding for Surgical Procedures.....	30
3.1.3 Follow-Up Visits.....	31
3.2 Rationale for Study Design and Control Group.....	31
3.3 Study Duration and Dates	32
4 STUDY POPULATION SELECTION	33
4.1 Study Population.....	33
4.2 Inclusion Criteria	33
4.3 Exclusion Criteria	33
5 STUDY TREATMENT(S).....	35
5.1 Description of Treatment(s).....	35
5.1.1 Study Drug.....	35
5.1.2 Placebo.....	35
5.2 Treatments Administered.....	35
5.2.1 Phase A (Initial Safety and PK Phase).....	35
5.2.2 Phase B (Treatment Phase)	35
5.3 Selection and Timing of Dose for Each Patient.....	35
5.4 Method of Assigning Patients to Treatment Groups.....	36
5.5 Blinding.....	36
5.6 Concomitant Therapy.....	36
5.7 Restrictions	36
5.7.1 Prior Therapy	36

5.7.2	Fluid and Food Intake	37
5.7.3	Patient Activity Restrictions	37
5.8	Treatment Compliance.....	37
5.9	Packaging and Labeling.....	37
5.10	Storage and Accountability.....	37
5.11	Investigational Product Retention at Study Site	37
6	STUDY PROCEDURES	39
6.1	Informed Consent.....	39
6.2	Medical History	39
6.3	Physical Examination.....	40
6.4	Vital Signs.....	40
6.5	Clinical Laboratory Tests.....	40
6.5.1	Laboratory Parameters	41
6.5.1.1	Safety Laboratory Tests	41
6.5.1.2	Coagulation Tests.....	42
6.5.1.3	Drug Concentration Tests	42
6.5.1.4	Immunogenicity Testing	42
6.5.1.5	Sample Storage	42
6.5.2	Sample Collection, Storage, and Shipping	42
6.6	Dispensing Study Drug	42
6.7	Pharmacokinetic Assessments	43
6.8	Efficacy Assessments.....	43
6.8.1	Efficacy Endpoint:	45
6.9	Adverse Events Assessments.....	46
6.9.1	Performing Adverse Events Assessments.....	46
6.9.2	Timing.....	47
6.9.3	Severity	47
6.9.4	Relationship	48
6.9.5	Expectedness.....	48
6.9.6	Clinical Significance.....	48
6.9.7	Clinical Laboratory Adverse Events.....	48
6.9.8	Serious Adverse Events	49
6.9.8.1	Definition	49
6.9.8.2	Reporting Serious Adverse Events	49
6.9.9	Treatment-Emergent Adverse Events	50
6.10	Concomitant Medication Assessments	51
6.11	Study Stopping Rules.....	51
6.12	Removal of Patients from the Trial or Study Drug.....	52
6.13	Replacement of Patients.....	52

6.14	Other Study Procedures	52
6.15	Appropriateness of Measurements.....	52
7	STUDY ACTIVITIES	53
7.1	Phase A: Initial Safety and PK Phase	53
7.1.1	Screening (Days -21 to -1).....	53
7.1.2	Visit 1 (Day 0) Procedures.....	53
7.1.2.1	Predose.....	53
7.1.2.2	Drug Administration (0 min)	53
7.1.2.3	10±2 min after start of infusion	54
7.1.2.4	30±5 min after start of infusion	54
7.1.2.5	1 hour ±10 minutes after start of infusion.....	54
7.1.2.6	2 hours ±10 minutes after start of infusion	54
7.1.2.7	4 hours ±10 minutes after start of infusion	54
7.1.2.8	8 hours ±10 minutes after start of infusion	54
7.2	Phase B: Treatment of a Bleeding Episode.....	54
7.2.1	Mild/Moderate Bleeding Episode Procedures	55
7.2.1.1	Pre treatment	55
7.2.1.2	Treatment (Time 0 hrs)	55
7.2.1.3	3, 6, 9, 12, 15, 18, 21 hours after first administration.....	55
7.2.2	Severe Bleeding Episode Procedures.....	56
7.2.2.1	Pre Treatment.....	56
7.2.2.2	Treatment (Time 0 hrs)	57
7.2.2.3	After first administration until improvement of the bleeding episode	57
7.2.2.4	During Continued Treatment	58
7.2.3	Rescue Treatment.....	58
7.3	Procedures at Follow-Up Visits in Phase B	59
7.3.1	3 Weeks (±2 days) visit.....	59
7.3.2	6 Weeks (±5 days) visit.....	59
7.3.3	12 Weeks (±5 days) visit.....	60
7.3.4	18 Weeks (±5 days) visit.....	60
7.3.5	24 Weeks (±5 days) visit.....	60
7.3.6	All Subsequent Visits 6 and 12 Weeks after Week 24 visit	61
7.3.6.1	6 Weekly (±5 days).....	61
7.3.6.2	12 Weekly (±5 days).....	61
7.3.7	End of Study Visit/Early Termination Procedures	61
8	QUALITY CONTROL AND ASSURANCE	63
9	PLANNED STATISTICAL METHODS	64
9.1	General Considerations	64
9.2	Determination of Sample Size	64
9.3	Analysis Populations.....	64

9.4	Demographics and Baseline Characteristics	65
9.5	Primary Endpoint	65
9.5.1	Primary Efficacy Endpoint	65
9.6	Secondary Endpoints	66
9.7	Tertiary Efficacy Endpoints	67
9.8	Safety Analyses	68
9.9	Pharmacokinetic Analyses	68
9.10	Other Analyses	69
9.11	Interim Analysis	69
10	ADMINISTRATIVE CONSIDERATIONS	70
10.1	Investigators and Study Administrative Structure	70
10.2	Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval	70
10.3	Ethical Conduct of the Study	70
10.4	Patient Information and Consent	71
10.5	Patient Confidentiality	71
10.6	Study Monitoring	71
10.7	Case Report Forms and Study Records	72
10.8	Data Monitoring Committee	72
10.9	Protocol Deviations	72
10.10	Criteria for Terminating Study	73
10.11	Criteria for Suspending/Terminating a Study Center	73
10.12	Access to Source Documentation	73
10.13	Data Generation and Analysis	73
10.14	Retention of Data	74
10.15	Financial Disclosure	74
10.16	Publication and Disclosure Policy	74
11	REFERENCE LIST	75

LIST OF IN-TEXT TABLES

Table 1.	Classification of severity of bleeding episodes	28
Table 2.	Total Amounts of Blood Taken During the Study	40
Table 3.	List of Laboratory Tests	41

LIST OF IN-TEXT FIGURES

Figure 1.	Study Design Flowchart	26
-----------	------------------------------	----

LIST OF APPENDICES

Appendix 1	Schedule of Events.....	77
Appendix 2	Sponsor Signatures.....	81

SYNOPSIS

Sponsor:

LFB USA Inc.

Name of Finished Product:

Coagulation Factor VIIa (Recombinant), LR769

Name of Active Ingredient:

Coagulation Factor VIIa (Recombinant), LR769

Study Title:

A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to <12 years old with Inhibitors to Factor VIII or IX: PerSept 2

Study Number:

LFB-FVIIa-007-14

Study Phase: Phase 3**Primary Objective(s):**

- To assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of LR769 for the treatment of bleeding episodes in hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors to factor VIII or IX
- To assess the safety of LR769, including the immunogenic potential of the drug product

Secondary Objective:

- To assess the pharmacokinetics (PK) of LR769 in hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors to factor VIII or IX, without a current bleeding episode

Other Objective:

- To assess the healthcare resource utilization of hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors treated with LR769

Study Design:

This is a global, multicenter, Phase III, Prospective, Open-Label, Randomized, Crossover Study.

After obtaining informed consent and performance of screening procedures, patients from birth to <12 years old who meet all inclusion and exclusion criteria will be randomized to start with one of two treatment regimens:

1. 75 µg/kg treatment regimen
2. 225 µg/kg treatment regimen

The assigned treatment regimen is the dose administered for initial assessment of safety and PK in Phase A and the starting dose in the treatment phase, Phase B. In addition, the

sampling regimen (sampling schedule 1: at 10 ± 2 minutes and 1 and 4 hours (± 10 minutes), and sampling schedule 2: at 30 ± 5 minutes and 2 and 8 hours (± 10 minutes) relative to the start of infusion of study drug) for the PK sampling is assigned. The study consists of two phases.

Phase A (Initial safety and PK phase): Depending on the treatment regimen to which patients are randomized, they will receive a single intravenous (IV) administration of either 75 $\mu\text{g/kg}$ or 225 $\mu\text{g/kg}$ of LR769 as a bolus injection administered in ≤ 2 minutes in a hospital setting or hemophilia treatment center. Patients must not be experiencing an active bleeding episode at that time and may not have received treatment with any factor VII(a) [FVII(a)] product within 24 hours prior to this administration. This administration is for the assessment of the safety of LR769. The patient will remain in the hospital or hemophilia treatment center and will be observed for any potential acute adverse event (AE) for at least 2 hours after dosing.

Pharmacokinetics:

During Phase A, approximately 12 patients from birth to < 6 years old and 12 patients ≥ 6 years old to < 12 years old, not currently experiencing a bleeding episode will, in addition to the safety assessments, have blood samples drawn for PK analysis during the initial administration of study drug. This is expected to result in at least 10 evaluable patients in each age group. PK sampling will be done according to the International Society of Thrombosis and Haemostasis (ISTH) guidance on PK studies (Lee et al., 2001). Samples will be taken pre-dose in all patients. To reduce the number of blood draws, subsequent sampling will be done in approximately half of the patients (sampling schedule 1) at 10 ± 2 minutes followed by 1 and 4 hours (± 10 minutes); the other half (sampling schedule 2) will be done at 30 ± 5 minutes followed by 2 and 8 hours (± 10 minutes) relative to the start of infusion of study drug.

Phase B (treatment phase): Patients who complete Phase A without any safety concerns will begin Phase B on a treatment schedule that consists of 12-week periods of treatment with the dose to which they were randomized. Depending on randomization, the treatment phase will begin with either 75 $\mu\text{g/kg}$ or 225 $\mu\text{g/kg}$ and each patient will subsequently “cross over” to the alternate treatment regimen every 12 weeks until the end of study (EOS). From 24 hours after the administration of LR769 in Phase A, patients are eligible to be treated with LR769 in the event of a bleeding episode.

Treatment of Mild/Moderate Bleeding Episodes:

Treatment of a mild/moderate bleeding episode will be initiated as soon as possible, but certainly within 4 hours of first symptoms of the onset of the bleeding episode. Treatment will consist of IV administration of either 75 $\mu\text{g/kg}$ or 225 $\mu\text{g/kg}$ (depending on randomization) of LR769 as a bolus injection administered in ≤ 2 minutes.

During the 75 $\mu\text{g/kg}$ treatment regimen, the initial 75 $\mu\text{g/kg}$ dose may be followed 3 hours ± 15 minutes later with 75 $\mu\text{g/kg}$ every 3 hours ± 15 minutes until the bleed is successfully treated. A maximum of 8 administrations in total over a 21-hour period are allowed in this

treatment regimen for mild/moderate bleeding episodes.

During the 225 µg/kg treatment regimen, the initial 225 µg/kg treatment may be followed 9 hours ± 15 minutes later with 75 µg/kg every 3 hours ± 15 minutes until the bleed is successfully treated. A maximum of 6 administrations in total within a 21-hour period are allowed in this treatment regimen for mild/moderate bleeding episodes.

If the bleeding episode is not successfully treated as assessed as an excellent or good response at 24 hours after the first administration, treatment with LR769 may not be continued and alternative treatment must be considered depending on the remaining symptoms (and be noted as concomitant medication). Treatment of this bleeding episode should not be continued with LR769 (study drug) in that case. The patient's physician may determine the best treatment in that case. This may be another bypassing agent [REDACTED] or other hemostatic treatment.

Patients are allowed to be treated for another bleeding episode in a different anatomical location within 24 hours after initial start of treatment, provided the response to treatment of the initial bleeding episode was either "good" or "excellent" and no more treatment is needed. Definition of the response categories is provided in Section 6.8. Occurrence of a bleeding episode in the same joint/anatomical location after 24 hours of the last treatment of the initial bleeding episode when an initial "good" or "excellent" response has been achieved will be treated as a new bleeding episode. If the bleeding episode occurs within 24 hours after the last treatment of the initial bleeding episode when an initial "good" or "excellent" response has been achieved, this is regarded as a true recurrence and therefore a treatment failure. There is no restriction on the number of bleeding episodes that can be treated with LR769 for each patient in this study. The use of LR769 for prophylaxis is not permitted.

Treatment of severe bleeding episodes:

Patients with a severe bleeding episode always need to be treated in a hospital or hemophilia treatment center. However, after consultation with the study staff, the first administration of LR769 for the treatment of a severe bleeding episode may be done at home, only if this patient has already completed Phase A.

Treatment of a severe bleeding episode will be initiated as soon as possible, but certainly within 4 hours of first symptoms of the onset of the bleeding episode. Examples of severe bleeding episodes are: central nervous system (CNS) hemorrhage, throat and neck hemorrhage, acute hemorrhage in the abdomen, and gastrointestinal (GI) bleeding. Additionally, bleeding episodes associated with significant blood loss or intolerable pain such as severe episodes of joint, muscle, and soft tissue bleeding episodes leading to significant joint damage and morbidity may qualify as a severe bleeding episode. Patients with severe bleeding episodes will be treated with 75 µg/kg or 225 µg/kg, depending on randomization and the 12-week regimen in which the patient is currently participating.

During the 75 µg/kg treatment regimen, the initial 75 µg/kg dose may be followed 2 hours later with 75 µg/kg every 2 hours ± 15 minutes until improvement of the bleeding episode is observed. The dose interval can then be increased to 3 hours ± 15 minutes for 1-2 days, after

which the interval may be increased to 4-12 hours \pm 15 minutes depending on the type of bleeding for as long as needed.

During the 225 μ g/kg treatment regimen, the initial 225 μ g/kg treatment may be followed 6 hours later with 75 μ g/kg every 2 hours \pm 15 minutes until improvement of the bleeding episode is observed. The dose interval can then be increased to 3 hours \pm 15 minutes for 1-2 days after which the interval may be increased to 4-12 hours \pm 15 minutes depending on the type of bleeding for as long as needed.

Rescue Treatment:

In case of an insufficient effect of LR769 (e.g., insufficient effect after 24 hours for a mild/moderate bleeding episode, or continued excessive bleeding in a severe bleeding episode), the treating physician should stop treatment with LR769 and treat the patient with another therapy, such as the treatment they used prior to enrollment in this study. This may be another bypassing agent [REDACTED] or other effective hemostatic treatment. The patient can return to treatment with LR769 for a new bleeding episode provided that at least 24 hours has passed since the other bypassing agent was given.

Prevention of Bleeding for Surgical Procedures:

While participating in this study, if a patient requires a surgical procedure or other intervention requiring prophylactic FVIIa treatment, then he may be enrolled in the LR769 surgical study (LFB-FVIIa-008-14), if he meets the entry criteria and if this study is open for enrollment in his age group and at the site. The LR769 surgical study could only include patients younger than 12 years of age if sufficient PK, efficacy and safety data becomes available and after the DMC has reviewed these data and determined the appropriateness of including this population. If the LR769 surgical study is not available at the site or the patient elects not to participate in the surgical LR769 study, or if an emergency surgical procedure needs to be performed, the patient will remain in this study and may be treated with the institution's standard of care for the procedure. In that case LR769 may NOT be used prophylactically or as treatment in the perioperative period. Use of all hemostatic agents will be recorded as concomitant medications and the reason for the procedure captured as an (S)AE as appropriate. After completion of the surgery and approval by the physician/investigator, the patient may re-start treatment in this study. The patient will be eligible again for treatment of bleeding episodes in the current study after a minimum of 24 hours following last administration of LR769 or another hemostatic product for the surgical procedure. The patient will continue in the dosing arm he was in prior to temporarily leaving the study to complete the 12 weeks of treatment in that regimen.

Follow-Up Visits:

Patients will be followed initially at 3 weeks \pm 2 days following the first administration in Phase A and subsequently every 6 weeks \pm 5 days. Patients may be treated for multiple bleeding episodes during the course of the study. All patients will be followed for at least 6 months after the first LR769 administration or, if the study ends, for 14 days (\pm 2 days) after the last administration of study drug.

Study Population:

Enrollment will continue until approximately 24 patients (12 patients from birth to <6 years old, and 12 patients ≥ 6 years old to <12 years old) have passed all screening procedures in the study and begun treatment. Patients in these age categories with congenital hemophilia A or B complicated by high-responding inhibitors (peak Bethesda Units [BU] ≥ 5) or lower-titer inhibitor refractory to increased dosing with factor concentrates may be enrolled. All grades of severity of hemophilia are allowed, as long as they have regular bleeding episodes and inhibitors, as evidenced by a BU ≥ 5 . Some patients may have lower detectable levels of inhibitors in the Bethesda assay, i.e., BU <5 but still cannot be treated with factor VIII or IX concentrates since they are known to have a strong memory (anamnestic) response after re-exposure to factor concentrates or, despite low titers of inhibitors, are still refractory to increased dosing with factor concentrates. These patients can therefore not be treated with these concentrates and may be included in this study. Only patients with at least 3 bleeding episodes of any severity in the 6 months prior to entry in the study will be enrolled; and patients <6 months of age with at least 3 bleeding episodes since birth will be enrolled. Patients receiving immune tolerance induction (ITI) therapy are allowed to be treated in the study as well if they have breakthrough bleeding episodes at a rate of at least 3 bleeding episodes in any severity within the last 6 months; if < 6 months old; at least 3 bleeding episodes in any severity since birth.

The study will continue until at least 352 mild/moderate bleeding episodes have been treated and at least 6 months have passed since first administration of LR769 in at least 22 patients (approximately 11 from each age group).

Diagnosis and Main Criteria for Inclusion**Inclusion Criteria**

To be eligible for enrollment into this study, patients must:

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 , OR
 - b. a BU <5 but expected to have a high anamnestic response to FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of factor VIII or IX products to treat bleeding episodes, OR
 - c. a BU <5 but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of factor VIII or IX products to treat bleeding episodes
3. be aged from birth to <12 years old
4. have experienced at least 3 bleeding episodes of any severity in the past 6 months; if < 6 months old, have experienced at least 3 bleeding episodes since birth
5. parents or legal guardians must be capable of understanding and be willing to comply with the conditions of the protocol
6. parents or legal guardians must have read, understood, and provided written informed consent

Exclusion Criteria

Patients will be excluded from participation in the study if any of the following criteria apply:

1. have any coagulation disorder other than hemophilia A or B
2. be immunosuppressed (i.e., the patient may not be receiving systemic immunosuppressive medication; CD4 counts at screening must be $>200/\mu\text{L}$)
3. have a known allergy or hypersensitivity to rabbits
4. have platelet count $<100,000/\mu\text{L}$
5. have had a major surgical procedure (e.g. orthopedic, abdominal) within 1 month prior to first administration of study drug
6. have received an investigational drug within 30 days of first study drug administration, or be expected to receive such drug during participation in this study
7. 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)
8. have an active malignancy (those with non-melanoma skin cancer are allowed)
9. have any life-threatening disease or other disease or condition which, in the investigator's judgment, could pose a potential hazard to the patient or interfere with the trial participation or trial outcome (e.g., a history of non-responsiveness to bypassing products or thromboembolic disease)
10. known or suspected hypersensitivity to the active substance or to any of its excipients

Test Product, Dose, and Mode of Administration:

Coagulation Factor VIIa (Recombinant), LR769.

LR769 will be administered IV at a dose of either 75 $\mu\text{g}/\text{kg}$ or 225 $\mu\text{g}/\text{kg}$ as a crossover treatment every 12 weeks, as multiple bolus doses, each administered in ≤ 2 minutes to treat mild/moderate bleeding episodes and severe bleeding episodes.

Reference Therapy; Dose; and Mode of Administration:

No reference therapy will be used.

Duration of Treatment:

In Phase A, patients will receive a single administration of study drug in a non-bleeding state. Patients are eligible for treatment of a bleeding episode 24 hours after the initial administration of LR769 in Phase A. Treatment for such bleeding episodes will continue until satisfactory resolution of the bleeding episode has occurred, but with a last administration of study drug no later than 21 hours after first treatment (with an efficacy assessment at 24 hours after initiation of treatment). Severe bleeding episodes may need to be treated for several days until the investigator determines the bleeding has stopped and the risk of recurrence of the bleeding is minimal.

Patients will be followed initially at 3 weeks ± 2 days, and 6 weeks ± 5 days following the first

administration in Phase A and subsequently every 6 weeks \pm 5 days. Patients may be treated for multiple bleeding episodes during the course of the study. All patients will be followed for at least 6 months after the first LR769 administration, or, in case the study ends, for 14 days (\pm 2 days) after the last administration of study drug.

The study will continue until at least 352 mild/moderate bleeding episodes have been treated and at least 6 months have passed since first administration of LR769 in at least 22 patients (approximately 11 from each age group).

The overall duration of the study is approximately 16 months from First Patient First Visit until Last Patient Last Visit. The enrollment period is expected to last approximately 9 months.

The duration of an individual patient's participation in this part of the study (from signing the informed consent form until the last study visit in Phase B) may vary from approximately 7 months to approximately 16 months depending on when the patient is enrolled, unless discontinued prematurely.

Pharmacokinetic Variables:

PK blood draws will occur for all patients while receiving treatment in Phase A in a non-bleeding state. FVIIa concentrations will be determined using a validated modified activity assay (Staclot[®] VIIa-rTF, Diagnostica Stago) at Good Biomarker Sciences (Leiden, The Netherlands).

PK data analysis will be performed using non-linear mixed effects modeling. The following parameters will be determined: clearance (Cl); volume of distribution (Vd); terminal half-life ($t_{1/2}$); area under the plasma concentration--time curve from time 0 to infinity ($AUC_{0-\infty}$); and maximum plasma concentration (C_{max}).

Efficacy Assessments:

Efficacy of the treatment of each bleeding episode will be assessed by the patient/parent ("parent" includes guardian and/or caregiver in the context of this protocol, with the understanding that "patient" participation depends on the patient's age and maturity). Efficacy categories (see Section 6.8) will be reviewed with the patient/parent at the first study visit. In case of treatment in the hospital, the physician will also assess the efficacy. Response to treatment will be rated as "none," "moderate," "good," or "excellent." None or moderate are usually followed by continued treatment with the study drug, good or excellent means that no further treatment is needed or, in case of a severe bleeding episode, the dosing interval can be increased. Additionally, the patient diary contains a Visual Analogue Scale (VAS) to rate the pain experienced by the patient will be completed by the same assessors as described above, to evaluate the response to treatment on pain.

Efficacy assessment of LR769 to treat a mild/moderate bleeding episode will occur within 15 minutes prior to each administration of study drug.

- Mandatory efficacy assessment timepoints for 75 μ g/kg – 3, 12, and 24 hours after

initial dose.

- Mandatory efficacy assessment timepoints for 225 µg/kg – 9, 12, and 24 hours after initial dose.

If additional administrations are needed after the initial injection then assessments are to be completed within 15 minutes prior to each subsequent injection.

Efficacy assessment of LR769 to treat severe bleeding episodes will be assessed within 15 minutes prior to each administration of study drug.

- Mandatory efficacy assessment timepoints for 75 µg/kg – 2, 12, and 24 hours after initial dose.
- Mandatory efficacy assessment timepoints for 225 µg/kg – 6, 12, and 24 hours after initial dose.

If additional administrations are needed after the initial injection then assessments are to be completed within 15 minutes prior to each subsequent injection.

The timepoint for the primary evaluation of efficacy will be 12 hours after first administration of study drug.

Efficacy Endpoint:

The primary efficacy endpoint for this study is defined as successful treatment of a bleeding episode at 12 hours after first administration of the study drug. The following are clarification definitions to satisfy regulatory requirements in multiple regions (i.e., the FDA and the EMA).

Definition of the primary efficacy endpoint for the FDA: the successful treatment of a bleeding episode at 12 hours after first administration of the study drug. For primary efficacy endpoint for the FDA, only treatment of mild/moderate bleeding episodes is taken into account. Severe bleeding episodes will be a minority of the bleeding episodes treated in the study, and will require treatment even if the bleeding has improved. Efficacy in severe bleeding episodes will be described separately. For primary efficacy endpoint for the FDA, successful treatment of a bleeding episode is defined as a combination of the following:

- *Good or Excellent* response noted by patient/parent/guardian, depending on patient's age and maturity
- Study drug treatment: No further treatment with study drug beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No other hemostatic treatment needed for this bleeding episode
- No administration of blood products indicating continuation of bleeding beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No increase of pain beyond timepoint where a Good or Excellent response for this

bleeding episode was noted that cannot be explained other than as continuation of bleeding

Definition of the primary efficacy endpoint for EMA: the proportion of bleeding episodes (mild/moderate and severe combined) with a “good” or “excellent” patient (for mild/moderate bleeding episodes) and physician (for severe bleeding episodes) reported assessment of efficacy at 12 hours after the first administration of study drug.

Secondary efficacy endpoints include:

- Proportion of mild/moderate bleeding episodes successfully treated, according to the same criteria as the primary endpoint of efficacy, at all other timepoints
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” patient (and/or physician when available) reported assessment of the efficacy at all timepoints
- Time to assessment of a “good” or “excellent” response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient/parent (and/or physician when available)
- The number of administrations and total amount of drug administered per bleeding episode

Tertiary efficacy endpoints include:

- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” physician-reported assessment of the efficacy at 12 hours (if available)
- Proportion of recurrences (defined as a bleeding episode in the same joint/anatomical location within 24 hours after an initial successful response)
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) requiring alternative treatment
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with successful pain relief

All assessments described as done by the patient may be done by the parent depending on the age of the patient.

Where applicable, analyses will be done for all patients and by age group (from birth to <6 years and ≥ 6 years to <12 years).

Safety Assessments:

Safety assessments on all patients will include physical examination, vital signs, clinical laboratory tests (serum chemistry, hematology/coagulation), immunology tests (including storage for potential future use). Safety assessments will be done at screening, at clinic visits 3 weeks (± 2 days), and subsequently every 6 weeks (± 5 days) following first administration

of study drug in this study in Phase A. Monitoring of AEs will occur continuously throughout the entire study.

Other Assessments:

As part of the healthcare resource utilization, data will be collected on use of product, number of visits to hospital, days of inpatient hospitalization, use of concomitant medication, and days away from school or work (if applicable) for patient/parent, due to bleeding.

Statistical Methods:

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

Analysis Populations:

The Enrolled Population will be defined as all patients who signed informed consent. Analyses of non-treatment emergent AEs (non TEAEs) will be done on the Enrolled Population.

The Safety Population will be defined as all patients who received treatment (either in Phase A and/or Phase B). All analyses of safety will be performed based on the Safety Population.

The Treated Population will be defined as all patients who received treatment for at least one bleeding episode, and each such bleeding episode will be analyzed as treated. All analyses of efficacy will be performed based on the Treated Population.

Pharmacokinetic analyses will be performed on the Evaluable PK Population, defined as all treated patients who have a post-injection Factor VIIa activity measurement.

Sample Size Determination:

The proportion (\hat{p}) of mild/moderate bleeding episodes treated with each dose of LR769 that are classified as being successfully treated will be compared with an objective performance criterion (OPC) of 0.55. A one-sided, one-sample normal approximation test, with an alpha = 0.0125 (adjusted from 0.025 to 0.0125 to account for multiplicity of testing), will be used to test the null hypothesis that $p \leq 0.55$ versus the alternative hypothesis that $p > 0.55$, where p is the true proportion of mild/moderate bleeding episodes that are classified as successes. This will be done for each treatment regimen.

With a true proportion of success of 0.70, a correlation among bleeding episodes for a given patient of 0.1, and an OPC of 0.55, a sample size of 22 patients with a total of 352 mild/moderate bleeding episodes (assuming 8 bleeding episodes per treatment regimen per patient) will provide statistical power $\geq 80\%$. The study will enroll at least 24 patients, to account for dropouts and potential unevaluable bleeding episodes.

Efficacy Evaluation:

The primary efficacy endpoint for this study is defined as successful treatment of a bleeding

episode at 12 hours after first administration of the study drug. The following are clarification definitions to satisfy regulatory requirements for the FDA and the EMA.

The definition of the primary endpoint for the FDA was established to satisfy the design requirements of the United States Food and Drug Administration (US FDA). For the primary efficacy endpoint for the FDA, only mild/moderate bleeding episodes are considered. The primary efficacy endpoint for the FDA is defined as successful treatment of a mild/moderate bleeding episode by 12 hours from initiation of treatment defined as meeting all of the following criteria:

- *Good* or *Excellent* response noted by patient/parent/guardian, depending on patient's age and maturity
- Study drug treatment: No further treatment with study drug beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No other hemostatic treatment needed for this bleeding episode
- No administration of blood products indicating continuation of bleeding beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No increase of pain beyond timepoint where a Good or Excellent response for this bleeding episode was noted that cannot be explained other than as continuation of bleeding

For each LR769 treatment, the proportion (\hat{p}) of mild/moderate bleeding episodes rated as successfully treated at 12 hours will be summarized using the count and percentage. A 95% normal approximation CI for the true percentage will be calculated taking into account the correlation between bleeding episodes for a given patient in calculating the standard error of the estimate \hat{p} .

The null and alternative hypotheses for the primary efficacy endpoint are as follows:

$$H_0: p \leq 0.55$$

$$H_1: p > 0.55$$

The null hypothesis will be tested using a one-sided, one-sample, normal approximation test and a test statistic obtained by dividing ($\hat{p} - 0.55$) by its estimated standard error, taking into account the correlation between bleeding episodes for a given patient. The test will be conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing). Treatment of mild/moderate bleeding episodes in the study with LR769 of a given dose will be regarded as successful if it is concluded that the true percentage of successfully treated bleeding episodes with that dose is greater than 0.55. The primary endpoint for the FDA was established to satisfy the requirements of the US FDA for the evaluation of success.

For primary efficacy endpoint for the EMA, the proportion of bleeding episodes (mild/moderate and severe combined) evaluated with a "good" or "excellent" response at 12 hours after first administration of the study drug will be calculated. This proportion of

success will be evaluated by the European Medicines Agency (EMA) as part of the assessment of the benefit:risk ratio for each dosing regimen.

In addition, the proportions of successfully treated mild/moderate bleeding episodes (according to the primary efficacy endpoint definition) will be compared between the two LR769 treatment dose regimens at a 2-sided alpha of 0.05.

The time to assessment of a “good” or “excellent” response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient/parent will be analyzed at the bleeding episode level using the Kaplan-Meier (K-M) method to estimate the survival distribution for this endpoint for each treatment regimen separately and combined. Patients who receive rescue medication will be considered failures and will be assigned a censored value of the final timepoint. Patients who do not achieve a “good” or “excellent” response will be censored at the time of last response.

For each treatment, the patient-level mean number of administrations and patient-level mean total amount of drug required per bleeding episode (mild/moderate and severe, separately and combined) will be summarized using descriptive statistics, and a 95% CI for the true mean (across patients) will be calculated based on normal approximation.

Safety evaluations:

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with any AEs, any serious AEs (SAEs), and any TEAEs will be presented for all patients and for the different dose regimens and for the Phase A and B separately. 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.

PK evaluations:

The Evaluable PK Population will be defined to be all treated patients who have a post-injection Factor VIIa activity measurement. Descriptive statistics for plasma concentrations at each timepoint and for PK parameters will be tabulated and plasma concentrations (FVIIa activity levels) over time will be graphically presented. A separate pharmacokinetic analysis plan (PKAP) will be written and signed off prior to performing the analyses.

Date of Original Approved Protocol: 30 April 2015

Date of Amendment 1: 04 August 2015 [REDACTED]

Date of Amendment 2: 26 August 2015

Date of Amendment 3: 09 October 2015

Date of Amendment 4: 29 June 2016

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AA	amino acid
AE	adverse event
ALB	albumen
ALT	alanine aminotransferase (SGPT)
aPCC	activated prothrombin complex concentrate
AST	aspartate aminotransferase (SGOT)
AUC _{0-∞}	area-under-the-concentration-versus-time curve from time 0 to ∞
BU	Bethesda units
CI	confidence interval
Cl	clearance
C _{max}	maximum concentration achieved
CNS	central nervous system
CRO	contract research organization
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOS	end of study
DMC	Data Monitoring Committee
DVT	deep vein/venous thrombosis
EGF	epidermal growth factor
EMA	European Medicines Agency
EU	European Union
EudraCT	European clinical trials database
FDA	Food and Drug Administration
FEIBA	FVIII Inhibitor Bypassing Activity
FVII	factor VII
FVIIa	factor VII activated
FVIII	factor VIII
FVIIIa	factor VIII activated
FIX	factor IX
FX	factor X
FXa	factor X activated
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
Hct	hematocrit
HEENT	Head, Eyes, Ears, Nose, Throat

Hgb	hemoglobin
HIV	human immunodeficiency virus
HTRS	Hemophilia and Thrombosis Research Society
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISTH	International Society of Thrombosis and Haemostasis
ITI	immune tolerance induction
IV	intravenous
K-M	Kaplan-Meier
LDH	lactic dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
OPC	Objective Performance Criterion
PKAP	pharmacokinetic analysis plan
PD	pharmacodynamics
pd	plasma derived
PE	pulmonary Embolism
PK	pharmacokinetics
PT	preferred term
rhFVIIa	activated recombinant human Factor VII
SAE	serious adverse event
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOC	system organ class
$t_{1/2}$	terminal half life
t_{max}	time at which maximum concentration is achieved
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USA	United States of America
VAS	visual analogue scale
Vd	volumes of distribution
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 [REDACTED], selected for the production of this complex human glycoprotein.

The investigational product is produced by recombinant DNA technology employing site-directed expression of the human factor VII (FVII) gene in the mammary gland of [REDACTED]. The transgene containing the human factor VII has been stably integrated into the genome of the [REDACTED]. The rhFVII gene is exclusively expressed by the mammary gland under the control of a beta-casein specific promoter. Milk from these [REDACTED] is collected and the FVII protein expressed is subsequently purified and activated during the purification process. The production of recombinant human factor VII in [REDACTED] 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.

Congenital Hemophilia

Hemophilia is an inherited coagulation disorder due to deficiency of either factor VIII (hemophilia A) (Patek and Taylor, 1937) or IX (hemophilia B) (Biggs et al., 1952). Reported prevalence of hemophilia is approximately 2 in 10,000 males globally, prevalence in developed countries has been reported as around 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 are usually 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 factor products that replace the deficient factor. However, the development of inhibiting antibodies to factors VIII and IX 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, have a family history of inhibitors, patients with 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 ITI therapy (Astermark, 2006). The *prevalence* of inhibitors to factor VIII or IX 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 (BU), 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) resulting in 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 who still do not respond sufficiently to (increasing doses of) factor VIII or IX 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 inhibitor patients. 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 site of bleeding. Thrombin (factor IIa) generation under normal circumstances is initiated 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 LA, 2009). A study looking at home treatment with 90 $\mu\text{g/kg}$ of NovoSeven[®] every 3 hours up to three 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 is dependent on the type and severity of the bleeding episode, but usually 90 $\mu\text{g/kg}$ administered every 2-3 hours is effective (NovoSeven[®] SmPC). Higher doses (e.g., 270 $\mu\text{g/kg}$) may also be utilized for treatment of mild-to-moderate bleeding episodes.

Short-term prophylactic treatment is 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 (Oberfell et al., 2008; Takedani et al., 2010).

Factor VIIa is also used for other bleeding disorders such as *acquired hemophilia* and *congenital factor VII deficiency*.

Background Information on the Product

LR769 is a recombinant human coagulation factor VIIa of the vitamin K dependent family of coagulation factors. In the presence of both calcium and phospholipids, factor VII/VIIa in a complex with Tissue Factor (TF) can activate factor X to factor Xa directly bypassing factor IX or factor VIII. 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 four distinct structural domains: the N-terminal γ -carboxylic-domain (GLA-domain), two epidermal growth factor (EGF) like domains and one serine protease domain. Activation of FVII into 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, initially, for the treatment of bleeding episodes and for the prevention of bleeding in surgical interventions or invasive procedures in congenital hemophilia A or B patients with inhibitors. The population foreseen is both adults and children.

At this time, there are no European Union (EU) or FDA guidelines for the development of factor VIIa 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 factor IX products (EMA/CHMP/BPWP/144552/2009). This guideline has been updated to include pediatric studies in conformance with the pediatric regulations. For this reason, a stepwise approach following the basic principles of the FIX Guideline has been adopted for purposes of preparing our 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 will evaluate two separate dose regimens of LR769: 75 $\mu\text{g/kg}$ and 225 $\mu\text{g/kg}$ for both mild/moderate and severe bleeding episodes in congenital hemophilia A or B patients with inhibitors ($\text{BU} \geq 5$) or with a known high anamnestic response or refractory to increased dosing of either FVIII or FIX, aged less than 12 years. Administration of LR769 will be repeated depending on the type and severity of the event.

Preliminary efficacy and safety results of a similar, ongoing, study in the same but older population (12 years and older) provide the basis for the current study. The available results of this other 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 Objectives

The primary objectives of this study are:

- To assess the efficacy of 2 separate dose regimens (75 µg/kg and 225 µg/kg) of LR769 for the treatment of bleeding episodes in hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors to factor VIII or IX
- To assess the safety of LR769. This includes the immunogenic potential of the drug product

2.2 Secondary Objective

The secondary objective of this study is:

- To assess the PK of LR769 in hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors to factor VIII or IX, without a current bleeding episode

2.3 Other Objective

- To assess the healthcare resource utilization of hemophilia A or B pediatric patients, from birth to <12 years old, with inhibitors treated with LR769

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

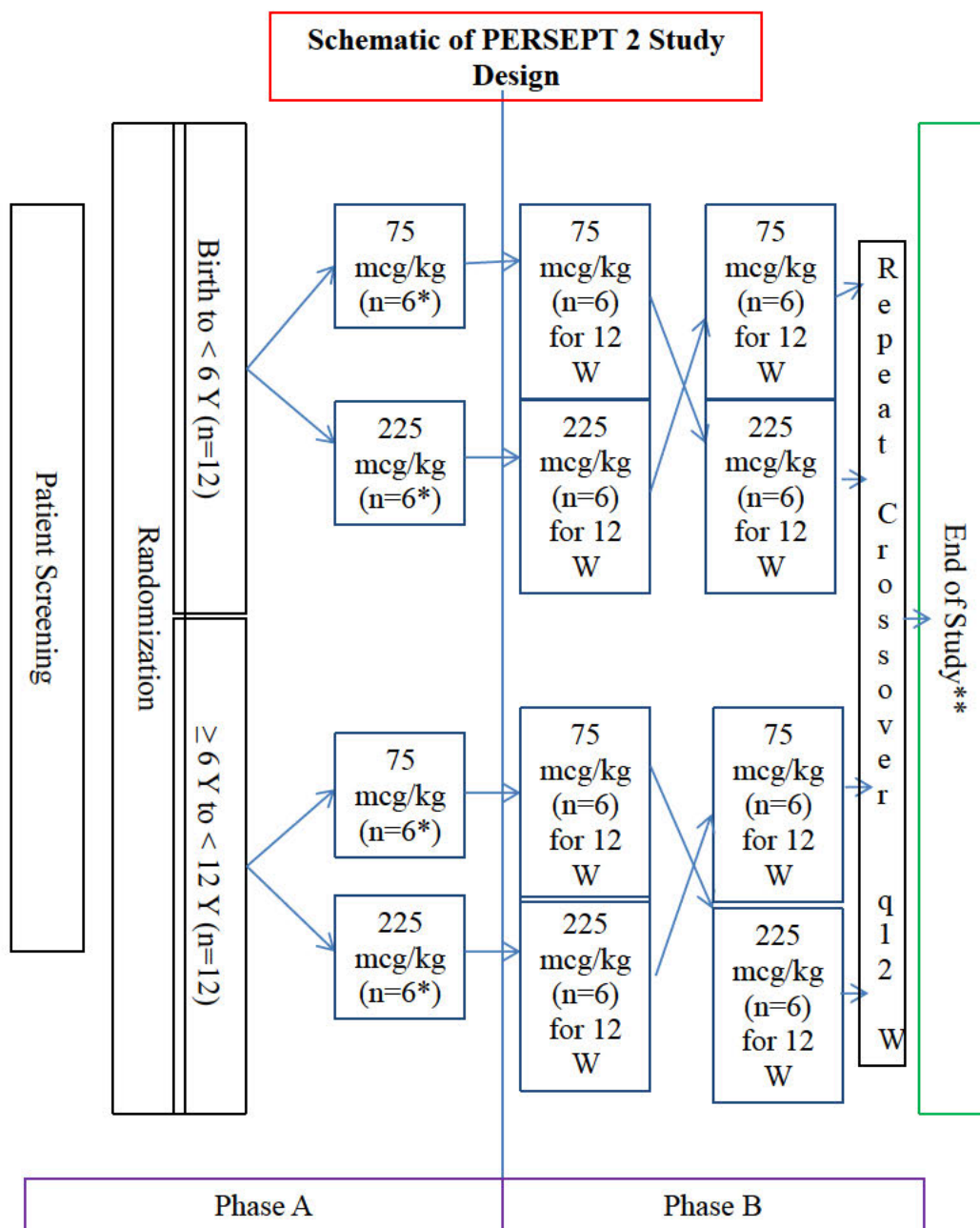
This is a global, multicenter, Phase III, prospective, open-label, randomized, crossover study. There are two patient age ranges (birth to < 6 years and ≥ 6 years to < 12 years); 12 patients will be enrolled within each age range.

After obtaining informed consent (from parents/guardians and assent of the patient if applicable) and performance of screening procedures, patients who meet all inclusion and exclusion criteria will be randomized to start with one of the two treatment regimens:

- 75 µg/kg treatment regimen
- 225 µg/kg treatment regimen

The assigned treatment regimen is the dose administered in the safety phase, Phase A, for the initial assessment of safety and PK, and the dose to be used when starting the treatment phase, Phase B, before crossover to the other treatment regimen (Figure 1).

Figure 1. Study Design Flowchart



* 3 Pts Randomized to Sampling Schedule 1 and 3 Patients to Sampling Schedule 2.
Y=year; W=week

** When last patient enrolled reaches 6 months after LR769 administration in Phase A

3.1.1 Phase A (Initial Safety and PK Phase)

Depending on randomization, patients will receive a single intravenous administration of either 75 µg/kg or 225 µg/kg of LR769 as a bolus injection administered in ≤2 minutes in a hospital setting or hemophilia treatment center. Patients must not have an active bleeding episode at that time and have not received treatment with any FVII(a) product within 24 hours prior to this administration. This administration is for the initial assessment of safety and PK of LR769. Patients will remain in the hospital or hemophilia treatment center and will be observed for any potential acute AE for at least 2 hours after dosing.

If the patient has a bleeding episode on the day of randomization prior to receiving study drug and therefore is unable to receive a first dose of LR769, but is otherwise eligible to receive the Phase A dose of LR769, he may receive this dose if the bleeding episode is resolved and after 24 hours have passed since his last hemostatic treatment.

Patients are eligible to be rescreened for a screening failure only if the patient was unable to be randomized during the 21 day screening period due to scheduling issues or due to bleeding.

Pharmacokinetics:

During Phase A, all patients will, in addition to the safety assessments, have samples drawn for PK analysis during the initial administration of the study drug (see the PK Analyses Section 9.9 for details). This is expected to result in at least 10 evaluable patients in each age group. PK sampling will be done according to the ISTH guidance on PK studies (Lee et al., 2001). Samples will be taken pre-dose in all patients. To reduce the amount of blood draws, subsequent sampling will be done in approximately half of the patients (sampling schedule 1) at 10±2 minutes, 1 and 4 hours (±10 minutes), and the other half of the patients (sampling schedule 2) at 30±5 minutes and 2 and 8 hours (±10 minutes) relative to the start of infusion of study drug. Population PK modeling will be used to analyze pharmacokinetics of LR769 in this pediatric population with this sparse sampling.

3.1.2 Phase B (Treatment Phase)

Patients who complete Phase A will start with a treatment regimen that consists of 12-week periods of treatment with a certain dose. Depending on randomization, the treatment regimen will start with either 75 µg/kg or 225µg/kg and patients will then cross over to the alternate treatment regimen every 12 weeks until the end of the study. From 24 hours after the administration of LR769 in Phase A, patients are eligible to be treated with LR769 in case they have a mild, moderate, or severe bleeding episode.

3.1.2.1 Classification of Severity of Bleeding Episodes

All levels of severity of bleeding episodes are allowed to be treated in this study. For the purposes of this study, mild, moderate and severe bleeding episodes are descriptively defined as presented in Table 1.

Table 1. Classification of severity of bleeding episodes

Bleeding Episode	Description	Examples
Mild	<ul style="list-style-type: none"> A bleeding that just starts and has little symptoms, i.e., little or no pain, little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity 	<ul style="list-style-type: none"> Early onset muscle and joint bleeds with no visible symptoms such as little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity Scrapes, superficial cuts, bruises, superficial mouth bleeds and most nose bleeds
Moderate	<ul style="list-style-type: none"> A bleeding that involves swelling or pain including some decrease in range of motion of affected joint (if joint bleeding event) or moderate decrease in mobility and activity 	<ul style="list-style-type: none"> Advanced soft tissue and muscle bleeds into the limbs Bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot or finger
Severe	<ul style="list-style-type: none"> Severe bleeds are potentially life/limb threatening, produce significant blood loss, pain, or can cause permanent nerve damage 	<ul style="list-style-type: none"> Mouth & neck region – Bleeding from the floor of the mouth, pharynx, or epiglottic area can result in partial or complete airway obstruction. Complicated joint bleeds – Hip joint or acetabular hemorrhages Iliopsoas hemorrhages Bleeding episodes leading to compartment syndrome such as in hand, wrists, forearm and anterior or posterior tibial compartments Central nervous system hemorrhages Gastrointestinal bleed – bleeding occurs in stomach or intestines Acute hemorrhage - such as bleeding into the abdomen Bleeding from major trauma

3.1.2.2 Treatment of Mild/Moderate Bleeding Episodes

Treatment of a mild/moderate bleeding episode will be initiated as soon as possible but certainly within 4 hours of first symptoms of the bleeding episode. Treatment will consist of

an IV administration of either 75 µg/kg or 225 µg/kg of LR769 as a bolus injection administered in ≤2 minutes.

During the 75 µg/kg treatment regimen, the initial 75 µg/kg dose may be followed 3 hours later with 75 µg/kg every 3 hours until the bleeding is successfully treated. A maximum of 8 treatments in total are allowed in this treatment regimen for mild/moderate bleeding episodes.

During the 225 µg/kg treatment regimen, the initial 225 µg/kg treatment may be followed 9 hours later with 75 µg/kg every 3 hours until the bleeding episode is successfully treated. A maximum of 6 treatments in total are allowed in this treatment regimen for mild/moderate bleeding episodes.

If the bleeding episode is not successfully treated as assessed as an excellent or good response at 24 hours after the first administration, treatment with LR769 may not be continued and alternative treatment must be considered depending on the remaining symptoms (and be noted as concomitant medication). Treatment of this bleeding episode should not be continued with LR769 (study drug) in that case. The patient's physician may determine the best treatment in that case. This may be another bypassing agent [REDACTED] or other hemostatic treatment.

Patients are allowed to be treated for another bleeding episode in a different anatomical location within 24 hours after initial start of treatment, provided the response to treatment of the initial bleeding episode was either "good" or "excellent". Occurrence of a bleeding episode in the same joint/anatomical location after 24 hours of the last treatment of the initial bleeding episode when an initial "good" or "excellent" response has been achieved will be treated as a new bleeding episode. If the bleeding episode occurs within 24 hours after the last treatment of the initial bleeding episode when an initial "good" or "excellent" response has been achieved, this is regarded a true recurrence and therefore a treatment failure. There is no restriction on the number of bleeding episodes that can be treated with LR769 for each patient in this study. The use of LR769 for prophylaxis is not permitted.

3.1.2.3 Treatment of Severe Bleeding Episodes

Treatment of a severe bleeding episode will be initiated as soon as possible, but certainly within 4 hours of first symptoms of the onset of the bleeding episode. Patients with severe bleeding episodes always need to be treated in a hospital or hemophilia treatment center. However, after consultation with the study staff, the first administration of LR769 for the treatment of a severe bleeding episode may be done at home but only if this patient already completed Phase A.

Patients with severe bleeding episodes will be treated with either 75 µg/kg or 225 µg/kg, depending on the randomization and 12-week period of crossover regimen they are in.

During the 75 µg/kg treatment regimen, the initial 75 µg/kg dose may be followed 2 hours later with 75 µg/kg every 2 hours until improvement of the bleeding episode is observed. The

dose interval can then be increased to 3 hours for 1-2 days after which the interval may be increased to 4-12 hours depending on the type of bleeding episode for as long as needed.

During the 225 µg/kg treatment regimen, the initial 225 µg/kg treatment may be followed 6 hours later with 75 µg/kg every 2 hours until improvement of the bleeding episode is observed. The dose interval can then be increased to 3 hours for 1-2 days after which the interval may be increased to 4-12 hours depending on the type of bleeding episode for as long as needed.

In case of continued excessive bleeding of a severe bleeding episode while treated with LR769, the patient's physician will decide the best treatment in that case. This may be another bypassing agent [REDACTED] or any other hemostatic treatment effective for inhibitor patients.

3.1.2.4 Rescue Treatment

In case of an insufficient effect of LR769 (e.g., insufficient effect after 24 hours for a mild/moderate bleeding episode, or continued excessive bleeding in a severe bleeding episode), the treating physician should stop treatment with LR769 and treat the patient with another therapy, such as the treatment they used prior to enrollment in this study. This may be another bypassing agent [REDACTED] or other effective hemostatic treatment. The patient can return to treatment with LR769 for a new bleeding episode provided that at least 24 hours has passed since the other bypassing agent was given.

3.1.2.5 Prevention of Bleeding for Surgical Procedures

While participating in this study, if a patient requires a surgical procedure or other intervention requiring prophylactic FVIIa treatment, then he may be enrolled in the LR769 surgical study (LFB-FVIIa-008-14), if he meets the entry criteria and if this study is open for enrollment in his age group and at the site. The LR769 surgical study could only include patients younger than 12 years of age if sufficient PK, efficacy and safety data becomes available and after the DMC has reviewed these data and determined the appropriateness of including this population. If the LR769 surgical study is not available at the site or the patient elects not to participate in the surgical LR769 study, or if an emergency surgical procedure needs to be performed, the patient will remain in this study and may be treated with the institution's standard of care for the procedure. In that case LR769 may NOT be used prophylactically or as treatment in the perioperative period. Use of all hemostatic agents will be recorded as concomitant medications and the reason for the procedure captured as an (S)AE as appropriate. After completion of the surgery and approval by the physician/investigator, the patient may re-start treatment in this study. The patient will be eligible again for treatment of bleeding episodes in the current study after a minimum of 24 hours following last administration of LR769 or another FVIIa product for the surgical procedure. The patient will continue in the dosing arm he was in prior to temporarily leaving the study to complete the 12 weeks of treatment in that regimen.

3.1.3 Follow-Up Visits

Patients will be followed initially at 3 weeks (± 2 days) and 6 weeks (± 5 days) following the first administration in Phase A and subsequently every 6 weeks (± 5 days). Patients may be treated for multiple bleeding episodes during the course of the study. All patients will be followed for at least 6 months after the first LR769 administration or, if the study ends, for 14 (± 2 days) after the last administration of study drug.

3.2 Rationale for Study Design and Control Group

At this time, there are no EU or FDA guidelines for the development of factor VIIa 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 factor IX products (EMA/CHMP/BPWP/144552/2009). 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 draft FIX Guideline has been adopted for purposes of preparing our 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 second in a series of three planned studies of rhFVIIa.

This is 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 treatment of a bleed, leading to potentially irreversible damage to the patient (mostly arthropathy), or could even be life-threatening depending on the location of the bleed. A comparison with current standard of care would then be the next best option, which, in this case, could be either 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.

For the primary efficacy endpoint for the FDA, efficacy will be evaluated by comparing the percentage of mild/moderate bleeding episodes that are evaluated as being successfully treated to an objective performance criterion (OPC). LR769 will be regarded as effective when the success percentage is statistically significantly higher than the OPC. This OPC was determined by reviewing the literature on what the reported success is of the treatment with bypassing agents. However, due to the use of a different endpoint in this study vs. several different other ones in literature, an estimate of what the OPC should be is difficult. Several publications provide a wide range of bleeding treatment success at different timepoints depending on the type of efficacy assessment used. An OPC of 55% was chosen, taking into account the stringent criteria for success (including elements to more objectively judge treatment success) in this study.

In addition, as the primary efficacy endpoint for the EMA, the proportion of bleeding episodes (mild, moderate and severe combined) evaluated with a “good” or “excellent” response as assessed by the patient/parent (mild/moderate bleeding episodes) and the

physician (severe bleeding episodes) at 12 hours after first administration of the study drug will be calculated.

3.3 Study Duration and Dates

The study will continue until at least 352 mild/moderate bleeding episodes have been treated and at least 6 months have passed for 22 patients since first administration of LR769, approximately 11 in each age group (birth to < 6 years and ≥ 6 years to < 12 years). First patient enrolled in the study is planned for the second half of 2015. The overall duration of the study up to and including Phase B is approximately 16 months from First Subject First Visit until Last Subject Last Visit. The enrollment period is expected to be approximately 9 months.

The duration of a patient's participation in the study (from signing the informed consent form until the last study visit in Phase B) may vary from approximately 7 months to approximately 16 months depending on when the patient was enrolled, unless discontinued prematurely.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study will enroll male congenital hemophilia A and hemophilia B pediatric patients from birth to <12 years old. All grades of severity of hemophilia are allowed, as long as they have regular bleeding episodes and inhibitors, as evidenced by a $BU \geq 5$. Some patients may have low levels of inhibitors i.e., a $BU < 5$ but still cannot be treated with factor concentrates since they are known to have a strong memory (anamnestic) response after re-exposure to factor concentrates. In other cases, patients with inhibitor levels < 5 BU, even after re-exposure to factor concentrates, may still be refractory to increased dosing with these factor concentrates. All of these patients therefore cannot be treated with these concentrates and need a bypassing agent, and are also allowed in the study. Patients on ITI therapy are allowed to be treated in the study as well, i.e., patients under this regimen are not excluded from the study, as long as they fulfill the criteria for inhibitors as described above and have regular bleeding episodes.

4.2 Inclusion Criteria

To be eligible for enrollment into this study, patients must:

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 $BU \geq 5$, OR
 - b. a $BU < 5$ but expected to have a high anamnestic response to FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of factor VIII or IX products to treat bleeding episodes, OR
 - c. a $BU < 5$ but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of factor VIII or IX products to treat bleeding episodes
3. be aged from birth to <12 years old
4. have experienced at least 3 bleeding episodes of any severity in the past 6 months; if <6 months old, have experienced at least 3 bleeding episodes since birth
5. parents or legal guardians must be capable of understanding and willing to comply with the conditions of the protocol
6. parents or legal guardians must have read, understood and provided written informed consent

4.3 Exclusion Criteria

Patients will be excluded from participation in the study if any of the following criteria apply:

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 $> 200/\mu\text{l}$)
3. have a known allergy or hypersensitivity to rabbits

4. have platelet count $<100,000/\mu\text{L}$
5. have had a major surgical procedure (e.g. orthopedic, abdominal) within 1 month prior to first administration of the study drug in this study
6. have received an investigational drug within 30 days of the first study drug administration, or is expected to receive such drug during participation in this study
7. have a clinically relevant hepatic (AST and/or ALT >3 times ULN) and/or renal impairment (creatinine >2 times ULN)
8. have an active malignancy (those with non-melanoma skin cancer are allowed)
9. have any life-threatening disease or other disease or condition which, in the investigator's judgment, could imply a potential hazard to the patient, or interfere with the trial participation or trial outcome (e.g., a history of non-responsiveness to bypassing products or thromboembolic disease)
10. known or suspected hypersensitivity to the active substance or to any of its excipients

Exclusion Criteria for PK portion:

Patients will not be included in the pharmacokinetic samplings process if they have had active bleeding and therefore received any hemostatically-active drugs within 24h prior to the administration of LR769. If so, their participation to the PK portion of the study will be delayed to a later date.

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

After obtaining informed consent of the parents/guardians and assent of the patient, if applicable, screening procedures are performed. Patients who meet all inclusion and exclusion criteria will be randomized to start with one of two treatment regimens:

1. 75 µg/kg treatment regimen
2. 225 µg/kg treatment regimen

The assigned treatment regimen is the dose administered in the safety phase, Phase A, for the initial assessment of safety and PK, and is the dose to be used when starting the treatment phase, Phase B, before crossover to the other treatment regimen.

5.2.1 Phase A (Initial Safety and PK Phase)

Depending on their randomization, patients will receive a single intravenous administration of either 75 µg/kg or 225 µg/kg of LR769 as a bolus injection in ≤ 2 minutes in a hospital setting or hemophilia treatment center in a non-bleeding situation. During Phase A, the initial administration of the study drug, patients will have samples drawn for PK analysis in addition to the safety assessments.

5.2.2 Phase B (Treatment Phase)

Patients who completed Phase A will start with a treatment regimen that consists of 12 week periods of treatment with a either dose of LR769. Depending on their randomization, the treatment schedule will start with either 75 µg/kg or 225µg/kg and they will cross over to the alternate treatment regimen every 12 weeks until the end of the study.

5.3 Selection and Timing of Dose for Each Patient

The treatment regimens used in this study are selected based on a Phase 1b study assessing the PK and pharmacodynamic (PD) effects of 3 doses of LR769 (25, 75, and 225 µg/kg) in hemophilia A or B patients. Safety and efficacy results of a study (RB-FVIIa-006-13,

PERSEPT 1) provide evidence that the 75 µg/kg every 3 hours treatment regimen and the 225 µg/kg dose (followed after 9 hours, if needed, by 75 µg/kg doses every 3 hours) supports and warrants further study of LR769 in younger paediatric patients. Available results of this study and of the Phase 1b study are described in the current LR769 Investigator's Brochure.

5.4 Method of Assigning Patients to Treatment Groups

After signing informed consent (and assent where applicable) and the completion of the screening procedures to confirm eligibility, patients will be randomized to one of the two treatment regimens by entering the patient details in a web based randomization system associated with the electronic Case Report Form (eCRF).

5.5 Blinding

Not applicable.

5.6 Concomitant Therapy

Restrictions to concomitant therapies are limited to the use of other sources of FVII(a), such as aPCC (FEIBA®) or NovoSeven®. These products must be avoided if at all possible, and may only be used for rescue therapy, in the event of an insufficient response to the study drug.

Other agents in the treatment of a bleeding episode, such as antifibrinolytics (e.g., aminocaproic acid or tranexamic acid) are allowed.

Patients on ITI therapy with FVIII or FIX products are allowed to be treated in the study as well, i.e., patients under this regimen are not excluded from the study, as long as they fulfill the criteria for inhibitors and frequency of break-through bleeding episodes as described in the inclusion criteria.

All concomitant medications need to be registered in the patients' files and/or patients' diaries and recorded in the eCRF.

5.7 Restrictions

5.7.1 Prior Therapy

The use of LR769 following the use of other bypassing agents [REDACTED] is only allowed when at least 24 hours have passed between the last administration of the drug and LR769 administration in both Phase A and Phase B. In case the use of these products was for treatment of a bleeding episode, that specific bleeding episode is not allowed to be treated with LR769 after being initially treated with a different therapeutic.

5.7.2 Fluid and Food Intake

No restrictions on fluid or food intake apply.

5.7.3 Patient Activity Restrictions

No restrictions on patient activity apply beyond any the patient may already be following.

5.8 Treatment Compliance

All patients will be treated in a hospital or hemophilia treatment center in Phase A of the study in a non-bleeding state. Compliance is then managed by the site staff who will record the exact dose and time of infusion. Compliance of treatment of bleeding episodes at home will be recorded by the patient/parent in a patient diary where the exact time of onset of a bleeding episode will be noted as well as the number of vials used and the amount administered at what time points to treat that bleeding episode. These data will be checked by the study staff at the next visit to the study center, and compared to the number of vials remaining at the patient's home.

5.9 Packaging and Labeling

The investigational product, LR769, will be supplied in clear glass vials as lyophilized powder of 1 mg and 5 mg. The vials will be labeled using multilingual labels, which will comply with local regulations and requirements. Vials will be packaged in an outer box. In addition, prefilled syringes with Water for Injection, as well as supplies for reconstitution and administration of the study drug will be provided.

5.10 Storage and Accountability

The investigational product, LR769, must be stored in a safe and secure place at the study center. The investigational product is to be stored at room temperature, is not to be frozen and should be protected from light. The Investigator is fully responsible for investigational product stored at the study center. Access should be strictly limited to the Investigator and designated staff. Neither the Investigator nor designated staff may provide investigational product to any patient not in the study. Dispensing of investigational product may be delegated, e.g., to a hospital pharmacy as locally applicable.

All investigational products received at the investigational site, dispensed to and returned from a patient will be documented on investigational product accountability forms. This documentation must be available for review by the monitor at the monitoring visit to confirm proper investigational product management.

5.11 Investigational Product Retention at Study Site

All used and unused vials of LR769 (Coagulation Factor VIIa [Recombinant]) will be retained until accountability has been performed by the monitor. For this purpose, patients will keep all used vials and bring them to the study center at each visit, where the study staff

will perform the treatment compliance check and store the vials for the accountability check by the monitor (unless local regulation does not allow this, in which case the containers should be stored as a 'surrogate').

All unused vials will be returned or destroyed according to the instructions of the Sponsor at the end of the study. Please refer to the pharmacy manual.

6 STUDY PROCEDURES

6.1 Informed Consent

All patients/parents 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 the patients' personal data, and that the patients' medical records may be reviewed for study purposes by authorized individuals other than their treating physician. It will be emphasized that the participation is voluntary and that the parent patient is allowed to refuse further participation in the protocol whenever he wants. Once the patient/parent completely understands the study and its procedures and risks he/she will be asked to sign and date the informed consent. No study procedures may begin prior to signing of the informed consent/assent document(s).

The patient may, depending on his age, receive age-appropriate information and 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 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

Once the informed consent has been signed and dated by the parents/guardians (and assent form by the patient, if applicable), the patient is considered enrolled in the study.

6.2 Medical History

The medical history of the patient will be obtained. Specific information will be recorded on the eCRF relating to any prior or existing medical conditions/surgical procedures involving the following: Infectious Diseases (including viral infections, like Hepatitis B and C and human immunodeficiency virus (HIV)), Allergies, Metabolic/Endocrine/Nutritional, Hematopoietic, Musculoskeletal, Dermatologic, Head, Ears, Eyes, Nose, and 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 will be collected. This will include the following: type of hemophilia (A or B), severity (including factor VIII or IX level), number of bleeding episodes during the past 6 months (if <6 months old, number of bleeding episodes since birth), existence of a target joint/bleeding site (i.e., a joint in which recurrent bleeding has occurred on four or more occasions during the previous 6 months or one in which 20 lifetime bleeding episodes have occurred), date of first detection of inhibitors, treatment for bleeding episodes (product and dose for each bleeding episode) in past month (or in case there were no bleeding episodes in the prior month, details from the last 2 bleeding episodes of the patient), ITI (current or in the past, including product, dose and dates of treatment).

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

6.3 Physical Examination

A standard physical examination will be performed at set timepoints during the study. All findings from this examination 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.

The patient will be weighed every 6 weeks and dose adjustment made if necessary.

When the standard physical exam is performed and at some additional timepoints, the patient will be checked for any signs of thromboembolic events such as pulmonary embolism (e.g., shortness of breath, chest pain, cyanosis), or deep venous thrombosis (e.g., calf pain, swelling/edema, redness, venous distension, pain on dorsiflexion).

6.4 Vital Signs

Vital signs will be obtained at set timepoints during the study. The assessments of vital signs 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 Clinical Laboratory Tests

Investigator will contact the Medical Monitor regarding any patient who weighs <12 kg 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.

For subjects < 12 kg, the minimum weight requirement is 10.5 kg ,when blood will be collected by peripheral venipuncture. The investigator must contact the Medical Monitor to discuss enrollment of any subject weighing < 12 kg with an indwelling catheter, Port-a-cath or PICC line. The following total amounts of blood will be taken at each visit as described in Table 2.

Table 2. Total Amounts of Blood Taken During the Study

Visit	Child weighs <12 kg at screening	Child weighs ≥12 kg to <19 kg at screening	Child weighs ≥19 kg at screening
Screening	7.5 mL	9.6 mL	15.2 mL
Visit 1	7.8 mL	9.6 mL	15.1 mL

Visit	Child weighs <12 kg at screening	Child weighs ≥12 kg to <19 kg at screening	Child weighs ≥19 kg at screening
Week 3	2.5 mL	2.5 mL	3 mL
Week 6	2.5 mL	2.5 mL	3 mL
Week 12	6.5 mL	7 mL	10 mL
Week 18	2.5 mL	2.5 mL	3 mL
Week 24	8 mL	9.7 mL	14 mL
Every 6 weeks after Week 24	2.5 mL	2.5 mL	3 mL
End of Study/Early Termination	8 mL	9.2 mL	15 mL

6.5.1 Laboratory Parameters

6.5.1.1 Safety Laboratory Tests

Clinical safety laboratory tests will include the following and will be carried out by the central laboratory for the study as presented in Table 3:

Table 3. List of Laboratory Tests

Hematology:	Serum Chemistry:
<ul style="list-style-type: none"> - Hematocrit (Hct) - Hemoglobin (Hgb) - Platelet count - White blood cell (WBC) count with differential (automated) - CD4 count¹ 	<ul style="list-style-type: none"> - Albumin (ALB) - Alkaline phosphatase (ALK-P) - Alanine aminotransferase (ALT; SGPT) - Aspartate aminotransferase (AST; SGOT) - Creatinine - Gamma-glutamyl transferase (GGT) - Lactate dehydrogenase (LDH) - Total protein
Coagulation <ul style="list-style-type: none"> - FVIII² or FIX³ - FVIII² or FIX³ inhibitors 	

¹ Only at Screening

² In hemophilia A patients only

³ In hemophilia B patients only

6.5.1.2 Coagulation Tests

Factor VIII (in hemophilia A patients) and factor IX (in hemophilia B patients) concentration will be assessed at Screening. The titer of inhibitors to factor VIII (in hemophilia A patients) or factor IX (in hemophilia B patients) will be assessed at Screening, 24 weeks, and EOT at the central laboratory. The Bethesda assay will be used for inhibitor testing.

6.5.1.3 Drug Concentration Tests

FVIIa concentration will be determined in all patients who have PK assessments done after receiving study drug in Phase A. The concentration will be determined by using a validated modified activity assay (Staclot[®] VIIa-rTF from Diagnostica Stago) in a single central laboratory.

6.5.1.4 Immunogenicity Testing

Serum samples to test for antibodies against LR769 and any host related impurities will be taken at set timepoints during the study. 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 identifying patients that are generating an immune response to milk proteins as a result of study drug treatment.

6.5.1.5 Sample Storage

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

6.5.2 Sample Collection, Storage, and Shipping

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

6.6 Dispensing Study Drug

When treatment is taking place in the hospital or hemophilia treatment center in Phase A, or for severe bleeding episodes in Phase B, drug will be prepared by and dispensed to the study staff according to the local study center's procedures. After the patient completes Phase A without any safety concerns, the patient/parent, after due training by the study staff, will receive study medication as well as materials for reconstitution and administration (e.g.,

alcohol swabs, syringes, butterfly needles, etc.) to store at home, in order to be able to treat subsequent mild/moderate bleeding episodes at home.

6.7 Pharmacokinetic Assessments

In Phase A, blood draws will occur at baseline (prior to LR769 administration) in all patients. To reduce the amount of blood draws, subsequent sampling will be done in approximately half of the patients (sampling schedule 1) at 10±2 minutes, 1 and 4 hours (±10 minutes), and the other half of the patients (sampling schedule 2) at 30±5 minutes and 2 and 8 hours (±10 minutes) relative to the start of infusion of study drug. FVIIa concentrations will be determined using a validated modified activity assay (Staclot® VIIa-rTF, Diagnostica Stago) at Good Biomarker Sciences (Leiden, The Netherlands).

6.8 Efficacy Assessments

Efficacy of the treatment of each bleeding episode will be assessed by the parent(s)/guardian or other caregiver in conjunction with the patient where possible (e.g., depending on age) and noted in the patient diary. In case of treatment the efficacy assessment in the hospital is also done by the physician and recorded in the patient's records. Response to treatment will be rated as "none," "moderate," "good," or "excellent,"

These are defined as follows:

- None: no noticeable effect of the treatment on the bleeding or worsening of patient's condition. Continuation of treatment with the study drug is needed.
- Moderate (fair): some effect of the treatment on the bleeding is noticed, e.g., pain decrease or bleeding signs improvement, but bleeding continues and requires continued treatment with the study drug.
- Good: symptoms of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) have largely been reduced by the treatment, but have not completely disappeared. Symptoms have improved enough to not require more infusions of the study drug.
- Excellent: full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage). No additional infusion of study drug is required.

Source: (Amby et al., 2009)

A response of none or moderate is usually followed by continued treatment with the study drug; a response of good or excellent means that no further treatment is needed or, in the case of a severe bleeding episode, the dosing interval can be increased. This four point scale is a frequently used tool in hemophilia to assess efficacy of treatment (Amby et al., 2009). If a bleeding episode is treated in the hospital, the physician will be asked to assess efficacy using the same scoring system at the same timepoints.

Additionally, as part of the patient diary, a VAS to rate pain will be completed by the parent/guardian/ caregiver in conjunction with the patient where possible (e.g., depending on age) to assess the response of pain to treatment.

Efficacy assessment of LR769 to treat a mild/moderate bleeding episode will occur within 15 minutes prior to each administration of study drug.

- Mandatory efficacy assessment timepoints for 75 µg/kg – 3, 12, and 24 hours after initial dose.
- Mandatory efficacy assessment timepoints for 225 µg/kg – 9, 12, and 24 hours after initial dose.

If additional administrations are needed after the initial injection then assessments are to be completed within 15 minutes prior to each subsequent injection.

Efficacy assessment of LR769 to treat severe bleeding episodes will be assessed within 15 minutes prior to each administration of study drug.

- Mandatory efficacy assessment timepoints for 75 µg/kg – 2, 12, and 24 hours after initial dose.
- Mandatory efficacy assessment timepoints for 225 µg/kg – 6, 12, and 24 hours after initial dose.

If additional administrations are needed after the initial injection then assessments are to be completed within 15 minutes prior to each subsequent injection.

The timepoint for the primary evaluation of efficacy will be 12 hours after first administration of study drug.

Patient diaries will be used for the collection of information on the efficacy of treatment, as assessed by the parent/guardian/caregiver in conjunction with the patient where possible (e.g., depending on age). Efficacy of treatment assessed by the physician during severe bleeding treatment in clinic will be documented in patient's source records.

In addition to the above score the following information will be collected for each bleeding episode (by patient for mild/moderate bleeding episodes and by physician for severe bleeding episodes treated onsite):

- Date and start time (first symptoms) of bleeding episode
- Cause of bleeding episode
- Severity of bleeding episode (according to Table 1)
- Type and anatomical site of bleeding episode
- In case of joint: target joint or not; specify joint

- Did any recurrence of bleeding episode (defined as bleeding in the same joint/anatomical location within 24 hours after an initial “good” or “excellent” response) occur
- Did the bleeding episode require any alternative treatment (including information on the nature of the alternative treatment, start date/time and stop date/time of alternative treatment, if applicable)
- Did the bleeding episode require visit to the hospital
- Occurrence of pain (prior to the 1st infusion of study drug to treat this bleeding episode) and progression/resolution of pain assessed at each efficacy assessment timepoint. Pain caused by a bleeding episode will be measured on a VAS in millimeters from 0 (no pain) to 100 (worst possible pain).
- Time to cessation of bleeding episode
- Date, dose and total volume, time of administration of each dose, lot numbers, and number of vials used.

All assessments described as done by the patient may be done by the parent/legal guardian or other caregiver depending on the age of the patient.

6.8.1 Efficacy Endpoint:

The primary efficacy endpoint for this study is defined as successful treatment of a bleeding episode at 12 hours after first administration of the study drug. The following are clarification definitions to satisfy regulatory requirements in multiple regions (i.e., the FDA and the EMA).

The primary efficacy endpoint for the FDA is defined as the successful treatment of a mild/moderate bleeding episode at 12 hours after start of treatment. Successful treatment of a mild/moderate bleeding episode is defined as a combination of the following:

- *Good or Excellent* response noted by patient/parent/guardian, depending on patient’s age and maturity
- Study drug treatment: No further treatment with study drug beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No other hemostatic treatment needed for this bleeding episode
- No administration of blood products indicating continuation of bleeding beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No increase of pain beyond timepoint where a Good or Excellent response for this bleeding episode was noted that cannot be explained other than as continuation of bleeding

The primary efficacy endpoint for the EMA is defined as the proportion of bleeding episodes (mild/moderate and severe combined) with a “good” or “excellent” patient (for mild/moderate bleeding episodes) and physician (for severe bleeding episodes) reported assessment of efficacy at 12 hours after the first administration of study drug.

Secondary efficacy endpoints include:

- Proportion of mild/moderate bleeding episodes successfully treated according to the same criteria as the primary endpoint of efficacy, at all other timepoints
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” patient (and/or physician when available) reported assessment of efficacy at all timepoints
- Time to assessment of a “good” or “excellent” response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient/parent (and/or physician when available)
- The number of administrations and mean total amount of drug administered per bleeding episode

Tertiary efficacy endpoints include:

- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” physician reported assessment of the efficacy at 12 hours (if available)
- Proportion of recurrences (defined as a bleeding episode in the same joint/anatomical location within 24 hours after an initial successful response)
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) requiring alternative treatment
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with successful pain relief

Where applicable, analyses will be done for all patients and by age group aged from birth to <6 years and ≥ 6 years to <12 years).

6.9 Adverse Events Assessments

6.9.1 Performing Adverse Events Assessments

An Adverse Event (AE) is defined as any undesirable physical, psychological or behavioral effect experienced by a patient 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 the study drug are also regarded AEs, but will be listed as *nonTEAEs*. Disease signs, symptoms, and/or laboratory abnormalities already existing prior to informed consent are not considered AEs, unless they reoccur after the patient has recovered from the pre-existing condition or they represent an exacerbation in severity, duration or frequency.

Bleeding episodes such as in the case of Hemophilia, which are the subject of this study are not regarded AEs. If a bleeding episode was caused by an injury, the injury should not be reported as an AE, unless it resulted in a medical finding other than a bleeding episode (e.g.,

scratch of skin). Therefore, any hemophilia-related events (e.g., hemarthrosis [presenting as swelling, pain, and limited motion], bruising, hemorrhages, or pain at bleeding site) will not be reported as AEs. However, the event may be regarded as an AE if it had occurred in a hemostatically normal patient under the same circumstances.

Hospitalization for the treatment of a bleeding episode regardless of severity, should not be reported as an AE.

All AEs will be recorded in 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 the investigational product, action taken, and outcome should be provided.

All AEs will be followed up until resolution or 30 days after EOS/Termination visit, whichever comes first.

6.9.2 Timing

Adverse events will be collected from the time of signing of the informed consent until completion of the study. At each study visit the patient/parent will be asked to report any and all changes in health status or condition (AEs) experienced since the previous visit. Additionally, the patient/parent will be asked specifically whether 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, redness, venous distension or pain on dorsiflexion of the foot.

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 the study drug. 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 drug administration and the occurrence of the event, the expected pharmacology of the study drug, the potential contribution of the underlying disease under investigation and/or any other concomitant diseases/medical history, evolution of the event when the drug was withdrawn and whether the event re-occurred 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, i.e., the Investigator's Brochure.

6.9.6 Clinical Significance

Clinical significance is defined as any variation in physical/laboratory findings 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 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 the deviation of the parameter.

6.9.8 Serious Adverse Events

6.9.8.1 Definition

A serious adverse event (SAE) is defined as any AE occurring at any dose that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events that may not result in one of the above may be considered SAEs 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 patient hospitalization, or the development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE.

6.9.8.2 Reporting Serious Adverse Events

The necessity and time requirements for reporting of 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 the study drug. If reporting via the eCRF is not available, the SAE may be recorded on the SAE form and 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 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 study drug 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 study drug, 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 Institutional Review Board (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 to notify the IRB/EC.

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

Any SAEs ongoing at the time of study termination will be followed until resolution or stabilization, with a maximum of 30 days after last study drug administration. Any SAE occurring within 30 days of the last dose of study drug will be reported even if the SAE occurs after the study has ended.

6.9.9 Treatment-Emergent Adverse Events

All AEs that occur after the first administration of the study drug will be regarded as treatment emergent. All AEs occurring from signing informed consent up to the first administration of the study drug will also be collected and will be referred to as non TEAEs.

A potential risk associated with the administration of Coagulation Factor VIIa (Recombinant) is the occurrence of an allergic 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 administration of the study drug to detect the occurrence of any potential allergic reaction. Symptoms of such 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 should 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, Coagulation Factor VIIa (Recombinant) 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 the study drug as well as during the follow-up visits to detect the occurrence of any thromboembolic events. Events that may occur are myocardial infarction, ischemic cerebrovascular accident, arterial thrombosis (e.g., aorta, intestinal), deep venous thrombosis (DVT), and pulmonary embolism (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, CT, 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.

In case an acute allergic reaction or a confirmed thrombotic event occurs in association with the administration of the study drug, such event should be reported in the same manner and timelines as a Serious Adverse Event (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 Concomitant Medication Assessments

All concomitant medication that was used by the patient during participation in the study will be recorded in the patients' files and/or patients' diaries and subsequently recorded in the eCRF. Specific emphasis will be put on the recording of concomitant medication for the treatment of bleeding episodes as well as for the treatment of pain. Patients who receive factor VIII or factor IX concentrates as part of either treatment of a bleeding episode or ITI therapy will maintain a detailed record of the actual treatment dates, times and doses.

6.11 Study Stopping Rules

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

- The Data Monitoring Committee (DMC) recommends after their scheduled review, or after an ad-hoc meeting in case of an SAE, that the study should be (temporarily) stopped
- A confirmed thrombotic event has been reported in any of the patients treated in the study
- An acute allergic 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.

6.12 Removal of Patients from the Trial or Study Drug

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, or
- A protocol deviation occurs that makes the interpretation of the data not feasible, or
- A clinically significant change in a laboratory parameter occurs that does not allow safe administration of the study drug and/or interferes with the interpretation of the study results, or
- Lack of compliance with study requirements, or
- The sponsor or investigator terminates the study, or
- The patient requests to be discontinued from the study.

In case of early withdrawal of the patient, he will be asked to perform the end of study visit assessments, unless he has withdrawn informed consent.

6.13 Replacement of Patients

Patients who are withdrawn will only be replaced if the minimum number of patients/bleeding episodes needed for Phase A or Phase B will not be met.

6.14 Other Study Procedures

For the healthcare resource utilization assessments, the direct healthcare costs will be determined by collecting data on use of product, number of visits to hospital/hemophilia treatment center, days of inpatient hospitalization and use of concomitant treatments. Secondary economic effects will be assessed by collecting data on days away from school or work.

6.15 Appropriateness of Measurements

Efficacy assessments are done according to existing guidelines and published literature. The patient/parent is the best person to assess the effect of the treatment on the bleed, as it most often is an internal bleeding episode in a joint or soft tissue.

Occurrence of pain and progression/resolution of pain is assessed at each efficacy assessment timepoint. Pain caused by a bleeding episode will be measured in the patient diary on a VAS in millimeters from 0 (no pain) to 100 (worst possible pain).

Analysis of concomitant medications will be performed in the trial with a focus on clotting factors (FVIII, FIX, FVIIa), blood products, analgesics, anti-inflammatory agents, and other drugs that may impair platelet and/or coagulation function.

7 STUDY ACTIVITIES

7.1 Phase A: Initial Safety and PK Phase

7.1.1 Screening (Days -21 to -1)

- Informed consent signature
- Determine eligibility
- Demographics (Date of birth, race/ethnicity, sex)
- Medical history
- Physical examination, including height and weight
- Safety labs (hematology, coagulation, chemistry), by central lab
- Vital signs
- Assessment of concomitant medication
- Assessment of AEs

7.1.2 Visit 1 (Day 0) Procedures

At randomization, patients will also be assigned to a specific PK sampling schedule. Half of the patients will be assigned to sampling schedule 1: at 10±2 minutes, 1 and 4 hours (±10 minutes). The other half will be assigned to sampling schedule 2: at 30±5 minutes and 2 and 8 hours (±10 minutes) relative to the start of infusion of study drug.

7.1.2.1 Predose

- Confirmation of eligibility (patient should not have received any FVIIa product within 24 hours prior to study drug administration)
- Physical examination
- Vital signs
- Randomization
- Blood sample for Pharmacokinetic Assessment
- Assessment of concomitant medication
- Assessment of AEs
- Immunogenicity sample

7.1.2.2 Drug Administration (0 min)

- A ≤2 minute IV push of 75 µg/kg or 225 µg/kg of LR769, depending on dosing randomization of the patient
- Assessment of AEs

7.1.2.3 10±2 min after start of infusion

- Blood sample for PK Assessment (when assigned to sampling schedule 1)
- Assessment of AEs

7.1.2.4 30±5 min after start of infusion

- Vital signs
- Blood sample for PK Assessment (when assigned sampling schedule 2)
- Assessment of AEs

7.1.2.5 1 hour ±10 minutes after start of infusion

- Vital signs
- Blood sample for PK Assessment (when assigned to sampling schedule 1)
- Assessment of AEs

7.1.2.6 2 hours ±10 minutes after start of infusion

- Vital signs
- Blood sample for PK Assessment (when assigned to sampling schedule 2)
- Assessment of AEs

7.1.2.7 4 hours ±10 minutes after start of infusion

- Vital signs
- Blood sample for PK Assessment (when assigned to sampling schedule 1)
- Assessment of AEs

7.1.2.8 8 hours ±10 minutes after start of infusion

- Vital signs
- Blood sample for PK Assessment (when assigned to sampling schedule 2)
- Assessment of AEs

7.2 Phase B: Treatment of a Bleeding Episode

Treatment of any bleeding episode will be initiated as soon as possible, but certainly within 4 hours of first symptoms of the onset of the bleeding episode.

7.2.1 Mild/Moderate Bleeding Episode Procedures

7.2.1.1 Pre treatment

- AE assessment
- Assessment of concomitant medication
- Bleeding Episode Characteristics
 - Location
 - Date/Time of start of bleeding episode
 - Severity
 - Spontaneous/traumatic
- Patient Diary

7.2.1.2 Treatment (Time 0 hrs)

- A ≤ 2 min IV push of 75 or 225 $\mu\text{g/kg}$ of LR769, depending on the dosing randomization of the patient and the 12 weeks treatment regimen he is in at the time of bleeding episode
- Record date, time and total dose of study drug as well as number and lot of vials used for preparation in patient diary (patient/parent); if in hospital or hemophilia treatment center in patient records by study staff
- AE assessment
- Assessment of concomitant medication

7.2.1.3 3, 6, 9, 12, 15, 18, 21 hours after first administration

- AE assessment (assessed over a period of 21 hours after first study drug administration, reported by the patient/parent in the patient diary if home treatment and in addition by study staff if in hospital or hemophilia treatment center)
- Efficacy assessments (within 15 minutes before each new administration of the study drug) to be done by the patient/parent if home treatment and by study staff if in hospital or hemophilia treatment center in addition to patient assessments
- Record date, time and outcome of the assessments in patient diary (patient/parent); if in hospital or hemophilia treatment center in patient records by study staff in addition to patient's assessment
- Assessment of concomitant medication

ADMINISTRATION OF STUDY DRUG:

When in 75 $\mu\text{g/kg}$ dose treatment regimen:

- If response to treatment 3 hours after last administration is unsatisfactory (i.e., efficacy assessment is not rated as good or excellent): a ≤ 2 min IV push of 75

µg/kg of LR769 may be administered. This may be repeated, if needed every 3 hours up to and including 21 hours after first administration.

- If response to treatment 3 hours after the first or any of the subsequent administrations is satisfactory (i.e., efficacy assessment is rated as good or excellent): no study drug administration. Perform the 3 hourly efficacy assessments until 3 hours after the last administration as well as the 12 hours efficacy assessments (if not already done).

When in 225 µg/kg dose treatment regimen:

- If response to treatment 9 hours after first administration is unsatisfactory (i.e., efficacy assessment is not rated as good or excellent): a ≤2 min IV push of 75 µg/kg of LR769 may be administered. This may be repeated, if needed every 3 hours up to and including 21 hours after first administration.
- If response to treatment 9 hours after first administration, or 3 hours after any subsequent administrations, is satisfactory (i.e., efficacy assessment is rated as good or excellent): no study drug administration. Perform the 12 hours efficacy assessments (if not already done).
- Record date, time and total dose of study drug as well as number and lot of vials used for preparation in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff.
- If, because of an initial sufficient response at 9 hours post initial dose of study drug, no additional study drug is administered, it may re-started before the 24-hour cut off in case of a recurrence of a bleeding episode. This should be noted in the patient's diary.

24 HOURS AFTER FIRST ADMINISTRATION

- AE assessment
- Efficacy assessments. If the response to treatment is still unsatisfactory (i.e., efficacy assessment is not rated as good or excellent): do not administer any more study drug. Alternative treatment should be initiated in consultation with the study staff.
- Record date, time and outcome of the assessments in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff in addition to patient's assessment
- Assessment of concomitant medication

7.2.2 Severe Bleeding Episode Procedures

Severe bleeding episodes always need to be treated in a hospital or hemophilia treatment center. Exception may be the first administration for the treatment of a bleeding episode, which can be done at home if the patient qualifies for that (see Section 3.1.2.3).

7.2.2.1 Pre Treatment

- AE assessment

- Assessment of concomitant medication
- Bleeding Episode Characteristics
 - Location
 - Date/time of start of bleeding episode
 - Severity
 - Spontaneous/traumatic
- Patient Diary

7.2.2.2 Treatment (Time 0 hrs)

- A ≤ 2 min IV push of 75 or 225 $\mu\text{g/kg}$ of LR769, depending on the dosing randomization of the patient and the 12 weeks treatment regimen he is in at the time of the bleeding episode
- Record date, time and total dose of study drug as well as number and lot of vials used for preparation in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff
- AE assessment
- Assessment of concomitant medication

7.2.2.3 After first administration until improvement of the bleeding episode

- AE assessment (reported by the patient/parent) in the patient diary and by study staff in the patient records in hospital or hemophilia treatment center)
- Assessment of concomitant medication
- Efficacy assessments (before each new administration of the study drug to be done by the patient/parent) if home treatment and by study staff if in hospital or hemophilia treatment center in addition to patient's assessments.
- Record date, time and outcome of the assessments in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff in addition to patient's assessment

ADMINISTRATION OF STUDY DRUG:

When in 75 $\mu\text{g/kg}$ dose treatment regimen:

- If response to treatment 2 hours after first or any subsequent administration is unsatisfactory (i.e., efficacy assessment is not rated as good or excellent): a ≤ 2 min IV push of 75 $\mu\text{g/kg}$ of LR769 may be administered.
- If 2 hours after last administration the bleeding episode has improved (i.e., efficacy assessment is rated at least as moderate): change to treatment at 3-hour intervals for 1-2 days until good or excellent result is reached
- After 1-2 days, the interval may be increased to 4-12 hours depending on the type of bleeding episode for as long as needed

When in 225 µg/kg dose treatment regimen:

- If response to treatment 6 hours after first administration is unsatisfactory (i.e., efficacy assessment is not rated as good or excellent): a ≤ 2 min IV push of 75 µg/kg of LR769 may be administered. This will be repeated every 2 hours until improvement in bleeding symptoms is observed
- If response to treatment after the first or any subsequent administration is satisfactory (i.e., efficacy assessment is rated as good or excellent): change to 3 hour intervals of treatment for 1-2 days
- After 1-2 days, the interval may be increased to 4-12 hours depending on the type of bleeding episode for as long as needed
- Record date, time and total dose of study drug as well as number and lot of vials used for preparation in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff.

7.2.2.4 During Continued Treatment

- AE assessment
- Assessment of concomitant medication
- Efficacy assessments:
 - before each new administration of study drug
 - at 12 and 24 hours after start of study drug treatment (if not done as part of pre administration assessment)
 - 12 hours after last study drug administration
- Record date, time and outcome of the assessments in patient diary (by the patient/parent); if in hospital or hemophilia treatment center in patient records by study staff in addition to patient's assessment
- Administration of study drug: continue with every 3 hours administration of a ≤ 2 min IV push of 75 µg/kg of rhFVIIa as long as indicated by the treating physician for 1-2 days, depending on the severity and location of the bleeding episode. The duration and treatment interval may be extended (up to every 4-12 hours) based on the judgment of the treating physician.
- Record date, time and total dose of study drug as well as number and lot of vials used for preparation in patient diary (by the patient/parent) if treatment is continued at home); if still in hospital or hemophilia treatment center in patient records by study staff

7.2.3 Rescue Treatment

In case of an insufficient effect of LR769 (e.g., insufficient effect after 24 hours for a mild/moderate bleeding episode, or continued excessive bleeding in a severe bleeding episode), the treating physician should stop treatment with LR769 and treat the patient with another therapy, such as the treatment they used prior to enrollment in this study. This may

be another bypassing agent [REDACTED] or other effective hemostatic treatment. The patient can return to treatment with LR769 for a new bleeding episode provided that at least 24 hours has passed since the other bypassing agent was given.

7.3 Procedures at Follow-Up Visits in Phase B

Timepoints of visits in Phase B are all relative to the first administration of LR769 in Phase A. The visits described in Sections 7.3.1 up to and including 7.3.6 may be conducted outside the hospital/hemophilia treatment center (e.g., when travel is too burdensome for the patient) by qualified site staff or qualified health care professionals on behalf of the site staff, provided all necessary arrangements for performing the assessments are available (blood collection, etc.).

In addition to the below schedule, site staff will contact the patient's parents approximately weekly to check the following:

- To confirm patient's compliance with the study treatment
- Collect information of bleeding episodes, whether any AEs occurred, study drug availability, etc.

7.3.1 3 Weeks (± 2 days) visit

- Check for physical signs of thromboembolic events
- AE assessment
- Assessment of concomitant medication
- Immunogenicity sample
- Patient diary check

7.3.2 6 Weeks (± 5 days) visit

- Check for physical signs of thromboembolic events
- AE assessment
- Assessment of concomitant medication
- Immunogenicity sample
- Weight and dose adjustment if necessary
- Drug accountability
- Patient diary check and collection
- Issue new diary

7.3.3 **12 Weeks (± 5 days) visit**

- Check for physical signs of thromboembolic events
- Safety labs (hematology, chemistry)
- Immunogenicity sample
- Weight and dose adjustment if necessary
- Crossover to alternative treatment regimen
- Vital signs
- AE assessment
- Assessment of concomitant medication
- Drug accountability
- Healthcare utilization assessments
- Patient diary check and collection
- Issue new diary

7.3.4 **18 Weeks (± 5 days) visit**

- Immunogenicity sample
- AE assessment
- Assessment of concomitant medication
- Check for physical signs of thromboembolic events
- Weight and dose adjustment if necessary
- Drug accountability
- Patient diary check and collection
- Issue new diary

7.3.5 **24 Weeks (± 5 days) visit**

- Immunogenicity sample
- Safety labs (hematology, chemistry)
- FVIII or FIX inhibitor sample for central lab
- Physical examination, including check for physical signs of thromboembolic events
- Weight and dose adjustment if necessary
- Vital signs
- AE assessment
- Healthcare utilization assessments
- Assessment of concomitant medication
- Drug accountability

- Patient diary check and collection
- Issue new diary

7.3.6 All Subsequent Visits 6 and 12 Weeks after Week 24 visit

7.3.6.1 6 Weekly (± 5 days)

- Immunogenicity sample
- AE assessment
- Assessment of concomitant medication
- Weight and dose adjustment if necessary
- Check for physical signs of thromboembolic events
- Drug accountability
- Patient diary check and collection
- Issue new diary

7.3.6.2 12 Weekly (± 5 days)

- Immunogenicity sample
- Check for physical signs of thromboembolic events
- Weight and dose adjustment if necessary
- Crossover to alternative treatment regimen
- Vital signs
- AE assessment
- Healthcare utilization assessments
- Assessment of concomitant medication
- Drug accountability
- Patient diary check and collection
- Issue new diary

7.3.7 End of Study Visit/Early Termination Procedures

- Immunogenicity sample
- Safety labs (hematology, chemistry)
- FVIII or FIX inhibitor sample for central lab
- Vital signs
- Physical examination, including check for physical signs of thromboembolic events
- AE assessment

- Healthcare utilization assessments
- Assessment of concomitant medication
- Drug accountability and patient diary collection

8 QUALITY CONTROL AND ASSURANCE

This study will be sponsored by LFB USA Inc. The sponsor will delegate specific tasks regarding the conduct of this study to a contract research organization (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

This section outlines the key components of the planned statistical analyses. Detailed methodology for the statistical analyses will be documented in a Statistical Analysis Plan (SAP). The SAP may modify the plan outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment. If after database lock changes are made to the SAP, these deviations will be documented in the Clinical Study Report (CSR).

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

Where applicable, analyses will be done for all patients and by age group (aged from birth to <6 years and ≥ 6 years to <12 years).

9.2 Determination of Sample Size

The proportion (\hat{p}) of mild/moderate bleeding episodes treated with each dose of LR769 that are classified as being successfully treated will be compared with an objective performance criterion (OPC) of 0.55. A one-sided, one-sample normal approximation test, with an alpha = 0.0125 (adjusted from 0.025 to 0.0125 to account for multiplicity of testing), will be used to test the null hypothesis that $p \leq 0.55$ versus the alternative hypothesis that $p > 0.55$, where p is the true proportion of mild/moderate bleeding episodes that are classified as successes. (Note: The standard error used in the denominator of the test statistic will account for the correlation among bleeding episodes for a given patient.) This will be done for each treatment regimen.

With the assumptions of a true proportion of success of 0.70, a correlation among bleeding episodes for a given patient of 0.1, and an OPC of 0.55, a sample size of 22 patients with a total of 352 mild/moderate bleeding episodes (assuming 8 bleeding episodes per treatment regimen per patient) will provide statistical power $\geq 80\%$. The study will enroll at least 24 patients, in order to account for dropouts and potential unevaluable bleeding episodes.

9.3 Analysis Populations

The Enrolled Population will be defined as all patients who signed informed consent. Analyses of non TEAEs will be done on the Enrolled Population.

The Safety Population will be defined as all patients who received treatment (either in Phase A and/or Phase B). All analyses of safety will be performed based on the Safety Population.

The Treated Population will be defined as all patients who received treatment for at least one bleeding episode, and each such bleeding episode will be analyzed as treated. All analyses of efficacy will be performed based on the Treated Population.

The Evaluable PK Population will be defined as all treated patients who have a post-study drug administration factor VIIa activity level. All PK analyses will be based on the Evaluable PK Population.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics for all patients, patients in the PK group and for patients in each dose group will be summarized using descriptive statistics for continuous variables and frequencies and percentages for categorical variables.

9.5 Primary Endpoint

9.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint for this study is defined as successful treatment of a bleeding episode at 12 hours after first administration of the study drug. The following are clarification definitions to satisfy regulatory requirements in multiple regions (i.e., the FDA and the EMA).

For primary efficacy endpoint for the FDA, only mild/moderate bleeding episodes are taken into account. Severe bleeding episodes will be a minority of the bleeding episodes treated in the study, and require further treatment even if the bleeding has improved. Efficacy in severe bleeding episodes will be analyzed separately, using descriptive statistics only.

The primary efficacy endpoint for the FDA is defined as the successful treatment of a bleeding episode at 12 hours (bleeding episode level), where a success is defined as meeting all of the following criteria:

- *Good or Excellent* response noted by patient/parent/guardian, depending on patient's age and maturity
- Study drug treatment: No further treatment with study drug beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No other hemostatic treatment needed for this bleeding episode
- No administration of blood products indicating continuation of bleeding beyond timepoint where a Good or Excellent response for this bleeding episode was noted
- No increase of pain beyond timepoint where a Good or Excellent response for this bleeding episode was noted that cannot be explained other than as continuation of bleeding

For each LR769 treatment, the proportion (\hat{p}) of mild/moderate bleeding episodes rated as successfully treated at 12 hours will be summarized using the count and percentage. A 95%

normal approximation CI for the true percentage will be calculated taking into account the correlation between bleeding episodes for a given patient in calculating the standard error of the estimate \hat{p} .

The null and alternative hypotheses for the primary efficacy endpoint are as follows:

$$H_0: p \leq 0.55$$

$$H_1: p > 0.55.$$

The null hypothesis will be tested using a one-sided, one-sample, normal approximation test and a test statistic obtained by dividing ($\hat{p} - 0.55$) by its estimated standard error, taking into account the correlation between bleeding episodes for a given patient. The test will be conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing). Treatment of mild/moderate bleeding episodes in the study with LR769 of a given dose will be regarded as successful if it is concluded that the true percentage of successfully treated bleeding episodes with that dose is greater than 0.55. The primary endpoint for the FDA is to satisfy the requirements of the US FDA for the evaluation of success.

No imputation of missing data will be performed for the primary analysis of the primary efficacy endpoint. However, two sensitivity analyses will be performed in order to examine the effect of missing data, if any, on the results of the primary analysis. In the first sensitivity analysis, all bleeding episodes for which the value of the primary efficacy endpoint is missing will be assigned as failures. In the second sensitivity analysis, all such bleeding episodes will be assigned as successes.

In addition, the proportions of successfully treated mild/moderate bleeding episodes will be compared between the two LR769 treatment doses at a 2-sided alpha of 0.05.

Two sensitivity analyses based on Generalized estimating equations (GEE) logistic regression analyses and Generalized linear mixed effects models (GLMM) will be used to assess the robustness of the result by accounting for the within-subjects correlation.

The primary efficacy endpoint for the EMA is defined as the proportion of bleeding episodes (mild/moderate and severe combined) with a “good” or “excellent” patient (for mild/moderate bleeding episodes) and physician (for severe bleeding episodes) reported assessment of efficacy at 12 hours after the first administration of study drug. This proportion of success will be evaluated by the EMA as part of the assessment of the benefit risk ratio for each dosing regimen.

9.6 Secondary Endpoints

The secondary efficacy endpoints consist of the following:

- Proportion of mild/moderate bleeding episodes successfully treated according to the same criteria as the primary endpoint of efficacy, at all other timepoints

- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” patient (and/or physician when available) reported assessment of efficacy at all timepoints
- Time to assessment of a “good” or “excellent” response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient (and/or physician when available)
- Descriptive analysis of the number of administrations and mean total amount of drug administered per bleeding episode

For each treatment regimen and both treatment regimens together, the proportions of bleeding episodes successfully treated, according to the same criteria as the primary endpoint of efficacy at all timepoints will be summarized using descriptive statistics, and a 95% CI for the true mean patient level proportion will be calculated based on normal approximation.

For each treatment regimen and both treatment regimens together, the proportions of bleeding episodes with a “good” or “excellent” patient reported assessment of the efficacy at all timepoints will be summarized using descriptive statistics, and a 95% CI for the true proportion will be calculated based on normal approximation.

The time to assessment of a “good” or “excellent” response of the bleeding episodes (mild/moderate and severe, separately and combined) by the patient/parent will be analyzed at the bleeding episode level using the K-M method to estimate the survival distribution for this endpoint for each treatment regimen separately and combined. Patients who receive rescue treatment at any time will be considered failures and will be assigned a censored value at the final timepoint. Patients who do not achieve a “good” or “excellent” response will be censored at the time of last response.

9.7 Tertiary Efficacy Endpoints

The tertiary efficacy endpoints consist of the following:

- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with a “good” or “excellent” physician reported assessment of the efficacy at 12 hours (if available)
- Proportion of recurrences (defined as a bleeding in the same joint/anatomical location within 24 hours after an initial successful response)
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) requiring alternative treatment
- Proportion of bleeding episodes (mild/moderate and severe, separately and combined) with successful pain relief

For each treatment, the mean number of administrations and mean total amount of drug administered per bleeding episode (mild/moderate and severe, separately and combined) will

be summarized using descriptive statistics. Also a 95% CI for the true mean will be calculated based on normal approximation.

9.8 Safety Analyses

All AEs will be coded using MedDRA. The number and percentage of patients with any AEs, any SAEs, and any TEAEs will be presented for all patients and for the different dose regimens and Phases A and B separately. 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 SOC and 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.

Descriptive statistics for the actual value at each timepoint and the change from baseline to each post-baseline timepoint in systolic and diastolic BP, heart rate, respiratory rate, and body temperature will be tabulated for each treatment. 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.

For continuous laboratory parameters, descriptive statistics for the actual value at each timepoint and the change from baseline (screening) to each post baseline timepoint will be tabulated for each treatment. Two-sided paired t-tests will be used to test whether the mean changes from baseline equal 0. Shift tables for laboratory parameters will be prepared.

9.9 Pharmacokinetic Analyses

A separate PKAP will be written and signed off prior to performing the analyses.

Descriptive statistics for plasma concentrations at each timepoint and for PK parameters will be tabulated and FVIIa concentration data (as measured by activity assay) over time will be graphically presented.

Pharmacokinetic data analysis will be performed using non-linear mixed effects modeling, which considers the repeated PK observations as a function of time using all available PK data collected in hemophilia patients who have received LR769 to date. Estimates and summary statistics of PK parameters (clearance, Cl; volume of distribution, Vd; terminal half-life, $t_{1/2}$; area under the plasma concentration-time curve from time 0 to infinity, $AUC_{0-\infty}$; and maximum plasma concentration, C_{max} . will be presented by dose group. The analyses will closely follow the guidelines of the US FDA and EMA for performing and reporting population PK analyses (FDA, 1999; EMA, 2007).

Analyses of the PK of LR769 in pediatric patients will be based on the evaluable PK population. It is expected that at least 10 of the 12 PK patients in each age group will be evaluable (for both PK assessments).

9.10 Other Analyses

A descriptive analysis of the healthcare utilization by patients treated with LR769 will be performed. For this purpose, data will be collected on use of product, number of visits to hospital, days of inpatient hospitalization, use of concomitant medication, and patient's days away from school or work (if applicable) for patient and parent/legal guardian due to bleeding episodes.

9.11 Interim Analysis

One interim analysis will be performed:

- Upon availability of FVIIa plasma activity data for at least 6 patients in each age group, PK profiles along with all safety and efficacy data available at that time will be reviewed by the DMC. Data will be used to identify any unexpected results that may impact safety or efficacy.
- At the time at least 80 bleeding episodes have been treated, data collected will be reviewed to identify any safety or efficacy issues.

The DMC will review these data and make recommendations to continue the study unaltered, or to make any modifications to the 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 Principal Investigator 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 Principal Investigator will review all study related documents including the protocol and the current version of the Investigator's Brochure. It is essential 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 must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the informed consent form. The Principal Investigator should 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 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 Good Clinical Practice: 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. Parent/legal guardian 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's parent/legal guardian in a language that is easily understood by the parent/legal guardian. 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/parent(s)/legal guardians agree 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 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 his parents/guardians may refuse to participate or withdraw from the study at any time and for any reason. Patients and/or their parents/guardians who participate in the study will be informed that information about them 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 to the study monitoring plan to ensure that all aspects of the current, approved protocol are being followed. Monitors will be given direct access to original source documents, which will be reviewed for 100% data verification captured in the eCRF. For this study, source documents include but are not limited to the Informed Consent Form, patient's medical records, patient diaries, laboratory results, reports of SAEs, 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 Principal Investigator must ensure the accuracy and completeness of the recorded data and provide his/her signature on the appropriate eCRFs and/or in the electronic system. The Investigator's electronic 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 DMC is responsible for the oversight of patient safety. The DMC will consist of three 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 efficacy, PK, and/or safety data at a minimum of the following timepoints:

- Each serious adverse drug reaction (i.e., an SAE for which at least a possible, probable, or definite causal relationship is assessed by the investigator and/or the sponsor)
- Quarterly: a concise cumulative listing of all SAEs (regardless of relationship to study drug) that occurred in the study
- After interim analysis specified in Section [9.11](#)

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 trial, 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 the primary endpoint, 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 at any time, 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 unplanned termination.

Possible reasons for unplanned study termination include but are not limited to:

- 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 the investigational product

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 critical 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, investigational product 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 (e.g., original laboratory reports etc.) 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 will maintain the trial documents as specified in ICH E6 Good Clinical Practice 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 Principal 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 the investigational product. These documents should 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 regulation 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 public databases 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.

11 REFERENCE LIST

Amby LK, Seremetis S, Obergfell A, Bjerre J (2009) Challenges of defining reliable clinical surrogate end points in haemophilia trials: a critical review. *Blood Coagul Fibrinolysis* 20:488-493

Astermark J (2006) Overview of inhibitors. *Semin Hematol* 43:S3-S7

Biggs R, Douglas AS, MacFarlane RG, Dacie JV, Pitney WR, Merskey (1952) Christmas disease: a condition previously mistaken for haemophilia. *Br Med J* 2:1378-1382

Hay CR, Brown S, Collins PW, Keeling DM, Liesner R (2006) The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 133:591-605

Key NS, Aledort LM, Beardsley D, Cooper HA, Davignon G, Ewenstein BM, Gilchrist GS, Gill JC, Glader B, Hoots WK, Kisker CT, Lusher JM, Rosenfield CG, Shapiro AD, Smith H, Taft E (1998) Home treatment of mild to moderate bleeding episodes using recombinant factor VIIa (Novoseven) in haemophiliacs with inhibitors. *Thromb Haemost* 80:912-918

Lee M, Morfini M, Schulman S, Ingerslev J (2001) Scientific and Standardization Committee Communication The Design and Analysis of Pharmacokinetic Studies of Coagulation Factors. ISTH org

Obergfell A, Auvinen MK, Mathew P (2008) Recombinant activated factor VII for haemophilia patients with inhibitors undergoing orthopaedic surgery: a review of the literature. *Haemophilia* 14:233-241

Patek AJ, Taylor FH (1937) Hemophilia. II. Some properties of a substance obtained from normal human plasma effective in accelerating the coagulation of hemophilic blood. *J Clin Invest* 16:113-124

Qaseem A, Snow V, Barry P, Hornbake ER, Rodnick JE, Tobolic T, Ireland B, Segal JB, Bass EB, Weiss KB, Green L, Owens DK (2007) Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians. *Ann Intern Med* 20;146:454-458

Stonebraker JS, Bolton-Maggs PH, Soucie JM, Walker I, Brooker M (2010) A study of variations in the reported haemophilia A prevalence around the world. *Haemophilia* 16:20-32

Takedani H, Kawahara H, Kajiwar M (2010) Major orthopaedic surgeries for haemophilia with inhibitors using rFVIIa. *Haemophilia* 16:290-295

White GC, Rosendaal F, Aledort LM, Lusher JM, Rothschild C, Ingerslev J (2001)
Definitions in hemophilia. Recommendation of the scientific subcommittee on factor VIII
and factor IX of the scientific and standardization committee of the International Society on
Thrombosis and Haemostasis. Thromb Haemost 85:560

Appendix 1 Schedule of Events

Phase A - Initial Safety and PK Phase

Evaluation	Screening Days -21 to-1	Pre- dose	0 min	10 ± 2 min.	30 ± 5 min.	1 hour ± 10 min.	2 hours ± 10 min.	4 hours ± 10 min.	8 hours ± 10 min.
Informed Consent	X								
I/E Criteria	X	X							
Demographics/Medical History	X								
Physical Examination ¹	X	X							
Clinical Laboratory Tests ^{2,5}	X								
Vital Signs	X	X			X ³	X ³	X ³	X ³	X ³
Randomization		X							
Drug Administration			X						
Concomitant Medication Assessment	X	X							
AE Assessment	X	X	X	X	X	X	X	X	X
Pharmacokinetic Assessments		X		X ⁴	X ⁴	X ⁴	X ⁴	X ⁴	X ⁴
Immunogenicity Sample ⁵		X							

¹ See Section 6.3 for physical examination assessments

² See Section 6.5 for clinical laboratory tests; CD4 will only be tested at Screening

³ For all patients, regardless whether PK sample is taken

⁴ Depending on assigned sampling schedule (half of the patients sampling schedule 1: at 10±2 minutes, 1 and 4 hours (±10 minutes), and the other half of the patients sampling schedule 2: at 30±5 minutes and 2 and 8 hours (±10 minutes) relative to the start of infusion of study drug)

⁵ Investigator will contact the Medical Monitor regarding any patient who weighs <12 kg for adaptation of the blood sample schedule to the patient's body weight

Phase B - Treatment of Mild/Moderate Bleeding Episodes

Evaluation	Mild/Moderate Bleeding Episode									
	Pre-treatment	0 hrs	3 hrs	6 hrs	9 hrs	12 hrs	15 hrs	18 hrs	21 hrs	24 hrs
Bleeding Characteristics ¹	X									
Drug Administration ²		X	X ³	X ³	X	X	X	X	X	
Efficacy Assessment ⁴			X	X	X	X ⁵	X	X	X	X ⁵
Patient Diary ⁶	X	X	X	X	X	X	X	X	X	X
AE Assessment	Throughout Study									
Conmed Assessment	Throughout Study									

¹ Includes location, date, time of start of bleeding, severity, spontaneous or traumatic

² Exact date, time and dose administered to be noted for each administration

³ No study drug administration when in the 225 µg/kg treatment regimen

⁴ Before each (planned) study drug administration and 3 hours after last

⁵ Always to be done, regardless of study drug administration

⁶ By the parent(s)/guardian or other caregiver in conjunction with the patient where possible (e.g., depending on age). Additionally, the site staff will collect their assessment in the patient's records (if applicable).

Phase B - Treatment of Severe Bleeding Episodes

Evaluation	Severe Bleeding Episode				
	Pre-treatment	0 hrs	q 2 hrs	q 3 hrs	q 4-12 hrs
Bleeding Characteristics ¹	X				
Drug Administration ²		X	X ⁵	X	X
Efficacy assessment ³			X	X	X
Patient Diary ⁴	X	X	X	X	X
AE Assessment	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X

¹ Includes location, date, time of start of bleeding, severity, spontaneous or traumatic

² Exact date, time and dose administered to be noted for each administration. Duration and interval of treatment upon judgment of the treating physician, depending on the type of bleeding

³ Prior to each (planned) study drug administration (initially every 2 hours when treated with 75 µg/kg, and at 6 hours after the initial 225 µg/kg administration). In case the treatment is continued beyond 24 hours, efficacy is assessed every 12 hours during the administration of study drug and 12 hours after last study drug administration.

⁴ By patient/caregiver at each study drug administration and efficacy assessment timepoint. Additionally the site staff will collect their assessment in the patient's records (as applicable).

⁵ No study drug administration and efficacy assessment at 2 and 4 hours if assigned to the 225 µg/kg treatment regimen

Schedule of Events (Phase B Follow-Up Visits)

	Following treatment in Phase A					Following 24 weeks visit		
Evaluation	3 wks ± 2 days	6 wks ± 5 days	12 wks ± 5 days	18 wks ± 5 days	24 wks ± 5 days	Every 6 wks ± 5 days	Every 12 wks ± 5 days	End of Study/Early Termination Visit
Physical Examination ¹	X ³	X ³	X ³	X ³	X	X ³	X ³	X
Safety Labs (Hematology, chemistry) ^{5,6}			X		X			X
Coagulation ^{5,6}					X ²			X ²
Adverse Event Assessment	Throughout Study							
Weight		X	X	X	X	X	X	
Vital Signs			X		X		X	X
Health Care Resource Utilization			X		X		X	X
Conmed Assessment	Throughout Study							
Check drug accountability and patient diary	X ⁴	X	X	X	X	X	X	X
Immunogenicity sample ⁶	X	X	X	X	X	X	X	X

¹ See Section 6.3 for physical examinations

² Inhibitor testing only

³ Only check for physical signs of thromboembolic events

⁴ Only check patient diary, no drug accountability

⁵ See Section 6.5.1 for clinical laboratory tests and coagulation tests; CD4 will only be tested at Screening

⁶ Investigator will contact the Medical Monitor regarding any patient who weighs <12 kg for adaptation of the blood sample schedule to the patient's body weight

Appendix 2 Sponsor Signatures

Study Title: A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Pediatric Patients from birth to <12 years old with Inhibitors to Factor VIII or IX: PerSept 2

Study Number: LFB-FVIIa-007-14

Original Protocol: 30 April 2015

Amendment 1 04 August 2015 [REDACTED]

Amendment 2 26 August 2015

Amendment 3 09 October 2015

Amendment 4 29 June 2016

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

