

COVER PAGE

TITLE: A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)

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LFB USA Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL LFB-FVIIa-008-14

A Phase 3 Study of the Safety and Efficacy of Coagulation Factor VIIa (Recombinant) for the Prevention of Excessive Bleeding in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX Undergoing Elective Surgery or Other Invasive Procedures (PERSEPT 3)

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CHANGE LOG

SAP Section Affected	Description:
3.2	<p>Descriptions of study treatment and dosing were revised slightly.</p> <p><i>Reason:</i> For consistency with the current version of the protocol, Amendment 4 dated 20 December 2016</p>
7.1	<p>A paragraph describing details of analysis on patient and on procedure level has been added.</p> <p><i>Reason:</i> As the study allows for multiple enrollment of the same patient, provisions need to be made for analysis of such cases.</p>
7.2	<p>A paragraph describing algorithm for deriving time points for post-operative assessments of efficacy has been added.</p> <p><i>Reason:</i> The CRF does not collect the exact timepoint for post-operative assessments, they are all marked with "EVERY 24 HOURS AFTER PROCEDURE COMPLETION" timepoint, which is insufficient for the analysis.</p>
7.3	<p>An algorithm for imputing missing responses at 48 hours timepoint with "Poor" has been added.</p> <p><i>Reason:</i> To clarify the cases, in which the primary efficacy endpoint is to be set to "Failure" when the 48 hour assessment is missing.</p>
7.7	<p>Added description of stratification of efficacy analyses by age group.</p> <p><i>Reason:</i> To include stratification by age for all efficacy endpoints and define the age groups.</p>

7.7.1	<p>A description of sensitivity analysis for the primary efficacy endpoint has been added</p> <p><i>Reason:</i> To introduce sensitivity analysis that treats missing primary efficacy endpoint as a failure.</p>
7.8	<p>Added description of stratification of safety analyses by age group.</p> <p><i>Reason:</i> To include stratification by age for all safety endpoints and define the age groups.</p>
7.8.2	<p>A clarification on how to assign adverse events to a specific procedure was added.</p> <p><i>Reason:</i> As the study allows for multiple enrollment of the same patient, provisions need to be made for analysis of such cases.</p>
7.9	<p>Removed stratification by age group for other endpoints.</p> <p><i>Reason:</i> Stratification by age for is not necessary for these additional endpoints.</p>
Throughout	<p>Several minor administrative changes throughout the document.</p> <p><i>Reason:</i> For consistency and clarity</p>

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LIST OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BU	Bethesda Units
CI	Confidence Interval
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FIX	Factor IX
FVII	Factor VII
ICH	International Conference on Harmonisation
ITI	Immune Tolerance Induction
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PICC	Peripherally inserted central catheter
PK	Pharmacokinetic
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event

TFL	Tables, Figures, Listings
US	United States
WHO DD	World Health Organization DD

1. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol LFB-FVIIa-008-14 Amendment 4 dated 20 December 2016, and electronic case report form (eCRF) dated 25 July 2016.

2. STUDY OBJECTIVES

2.1 *Primary Objective*

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

2.2 *Secondary Objective*

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

3. STUDY DESCRIPTION

3.1 *Study Design*

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

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

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

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

Postoperative Efficacy Assessments: Efficacy assessments will be completed every 24 (± 2) hours and at last administration of LR769. The patient's postoperative response to treatment with LR769 will be assessed by the investigator or designee and recorded as "excellent," "good," "moderate," or "poor". If the patient is discharged while on treatment,

these assessments will be done via telephone. The final assessment (which represents the primary efficacy outcome) will be performed by the investigator at the study center 48 (\pm 4) hours after last dose of LR769 and will be based upon the totality of assessments performed on the patient at each timepoint.

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

3.2 Study Treatment

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

3.2.1 Treatment for Major Surgical Procedures

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

Table 1. Doses and Dosing Schedule for Major Surgical Procedures:

Day	Dose	Recommended Frequency
Day 0 (before surgical incision or invasive procedure)	200 μ g/kg	Initial dose
Day 0 (post first dose) – 48 hours	75 μ g/kg	Every 2 hours (\pm 5 minutes)
Days 3- 4	75 μ g/kg	Intervals of up to every 4 hours but not more frequently than every 2 hours

Days 5-6	75 µg/kg	Intervals of up to every 6 hours but not more frequently than every 2 hours
Days 7-10	75 µg/kg	Intervals of up to every 8 hours but not more frequently than every 2 hours
Day 11 to Last Administration of LR769	75 µg/kg	Intervals of up to every 12 hours but not more frequently than every 2 hours

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

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

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

3.2.2 Treatment for Minor Surgical or Other Invasive Procedures

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

Table 2. Doses and Dosing Schedule for Minor Surgical or Other Invasive Procedures

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

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

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

3.2.3 All Procedures

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

3.3 Data Monitoring Committee (DMC)

A DMC is responsible for the oversight of patient safety. Details of DMC activities will be documented in a separate DMC Charter.

4. SAMPLE SIZE AND POWER CALCULATION

The sample size was determined based on adaptations of international guidelines for coagulation factors and after United States (US) and European Union (EU) health authority consultations. The study will continue until at least 12 surgical procedures (including a minimum of 6 major surgeries, of which at least 5 must be procedures other than central venous access device placement) have been performed in at least 6 patients.

5. ANALYSIS ENDPOINTS

Primary Efficacy Endpoint

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

Secondary Efficacy Endpoints

- Percentages of success as defined as the combination of "good" and "excellent" responses by the investigator or designee for all efficacy timepoints other than the primary
- Percentages of "poor," "moderate," "good," and "excellent" response by the investigator or designee for all efficacy timepoints
- Percentages of success as defined as the combination of "good" and "excellent" responses by the surgeon/practitioner

- Percentages of “poor,” “moderate,” “good,” and “excellent” response by the surgeon/practitioner for the intraoperative period
- Intraoperative blood loss determined by the surgeon/practitioner as compared to the surgeon/practitioner’s maximum predicted blood loss
- Number of events requiring transfusion between start of procedure and 48 (\pm 4) hours after last administration of LR769
- Changes in hemoglobin between start of procedure and 48 (\pm 4) hours after last administration of LR769
- Amount of LR769 used. Total, and separated by use in hospital, at home, or for specific reasons (eg, physical therapy, or other reasons like drain or suture removal)
- Number and type of bleeding episodes at the surgical site between start of procedure and 48 (\pm 4) hours after last administration of LR769
- Number of surgical interventions/re-explorations for bleeding episodes between start of procedure and 48 (\pm 4) hours after last administration of LR769

Safety Endpoints

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

Other safety assessments on all patients will include physical examination, vital signs, clinical laboratory tests (serum chemistry, hematology/coagulation).

6. ANALYSIS POPULATIONS

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

The Safety Population is defined as all patients who receive at least 1 dose of LR769. All safety analyses will be performed on the Safety Population.

Baseline characteristics will be summarized for both the Safety and the Efficacy populations.

7. ANALYTICAL PLAN AND STATISTICAL METHODS

7.1 General Conventions and Statistical Considerations

All statistical analyses will be performed and data appendices will be created using the SAS system version 9.4 or higher.

Data collected in this study will be presented in summary tables and patient data listings. Summary descriptive statistics for continuous variables will include the number of observations with non missing values, number of observations with missing values, mean, standard deviation (SD), median, and minimum and maximum values. All raw data will be presented to the original number of decimal places. Means, medians, quartile 1 (Q1), and quartile 3 (Q3) will be presented to 1 more decimal place than in the raw data. Standard deviations will be presented to 2 more decimal places than in the raw data. All data collected will be presented in the data listings.

Summary tables for categorical variables will include the number and percentage of observations for each category. If not specified additionally, the number of observations with non missing values will be the denominator for percentage calculation.

Unless otherwise stated, all statistical tests will be performed using 2-sided tests at the 5% significance level. P-values less than 0.001 will be displayed as <0.001 in the outputs.

Analyses will be stratified by the type of surgery (Minor/Major).

The protocol allows for one patient to enter the study more than one time (for different procedures). Baseline characteristics and demography data will be summarized on a patient level, while efficacy and safety assessments are to be analyzed on a procedure level. Procedure characteristics and disposition will also be summarized on a procedure level. When performing analysis on a patient level, the first value observed for a patient is to be reported (for instance, age that was recorded during the first procedure for the patient will be summarized in the demographics). All tables will contain explicit footnotes to describe on what level the data are summarized.

If necessary, the analytical plan and statistical methods section may be updated before the database lock. Any changes in statistical methods that may have an impact on the primary conclusions drawn from this clinical trial will be described in an amendment to the protocol. All other changes in the statistical plan will be described in section 9.8 of the clinical study report (CSR). An explanation will be provided for deviations from the planned analysis.

7.2 Definition of Baseline, Study Visits, and Visit Windows

Baseline is defined as the last available assessment prior to first study drug dose.

For Post-Operative assessments timepoints will be assigned according to Protocol-specified visit windows. Assessment occurring 24 (\pm 2) hours from procedure completion will be assigned to the 24-hour timepoint, and so on every 24 hours, creating timepoints for 48, 72... hours.

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

7.3 Handling of Missing Data

Any imputation of missing or incomplete data will be flagged in the analysis datasets. The original value will be kept for traceability.

Missing Final Assessment of Postoperative Response (48 [\pm 4] hours after the last dose of LR769)

In accordance with the definition of postoperative assessment in section 6.8 of the Protocol, missing final postoperative assessment of treatment response by the investigator will be imputed to "Poor", if and only if, both of the following conditions are satisfied: (1) patient was withdrawn from study, within 2 days after the last dose of LR769, due to adverse event or by Investigator's decision and (2) rescue therapy (any medication in antihemorrhagics ATC subgroup) was used within 52 hours after the last dose of LR769.

Incomplete/Missing Dates

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

The following rules will be applied for AEs and concomitant medications with incomplete dates:

- If Day is missing for Start Date and Month and Year are the same as Month and Year for the First Treatment Date, then Start Date equals First Treatment Date.
- If Day is missing for Start Date and Month and Year are not the same as Month and Year for the First Treatment Date, then impute Day 1 of the month.
- If Day and Month are missing for Start Date and the Year is the same as the Year for the First Treatment Date, then Start Date equals First Treatment Date.
- If Day and Month are missing for Start Date and the Year is not the same as the Year for the First Treatment Date, then impute July 1st of the year.

- If the Start Date is missing entirely, impute the start date with minimum between the End date of AE and First Treatment Date. Therefore, if an AE with missing start date has ended before the start of the treatment, the Start Date will be imputed with the End Date, and if the AE in question ended after the First Treatment Date, then the Start Date will be imputed with the First Treatment Date.

No imputation for the end date of AEs will be done. However, the end date of concomitant medications will be imputed as the last day of the month if only the day is missing, and as December 31st of the year if both the day and the month are missing.

No other imputation of missing data will be done.

7.4 Patient Disposition

The number of screened patients will be summarized. For screen failures, the reason for screen failure will be summarized using counts and percentages.

The number of enrolled patients will be summarized along with the number and percentage of enrolled patients in the Safety and Efficacy Populations, completing the study, withdrawing from the study and the primary reason for withdrawal, and the number of deaths. Number of patients previously enrolled in PERSEPT 1, PERSEPT 2 and PERSEPT 3 studies will also be summarized. Analyses will be stratified by type of surgery and overall.

7.5 Protocol Deviations

Deviations from the protocol will be recorded in the electronic data capture (EDC) and reviewed on a monthly basis by Medical Monitors. Listing of all protocol deviations will be created.

7.6 Patient Characteristics

7.6.1 Baseline and Demographic Characteristics

All baseline characteristics will be summarized by surgery type and overall for the Safety and Efficacy Population. The analysis will then be repeated stratifying by age group (< 12 years and ≥ 12 years). The following parameters will be summarized:

- Age
- Race
- Ethnicity
- Sex

- Weight at baseline
- Height at baseline
- Body mass index (BMI) at baseline
- Vital Signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, etc...) at baseline
- 12-Lead electrocardiogram (ECG) at baseline
- Physical Examination at baseline

No hypothesis testing is planned for baseline characteristics, so the analysis will be purely descriptive.

Listings of baseline characteristics will also be created.

7.6.2 Medical History and Concurrent Medical Conditions

Medical history will be summarized by type of surgery and overall. The number of patients with prior and concurrent conditions by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) will be output. A condition will be considered prior if its start date is before the first injection of study drug. A condition is considered concurrent if its end date is after the first injection of study drug or missing, and its start date is before the last injection of study drug.

Listing of prior and concurrent medical conditions will be created.

Disease history data will also be summarized by type of surgery and overall. The following parameters will be included in the summary: type of hemophilia, hemophilia severity grade at screening, factor level (%), Inhibitor status (Bethesda units [BU] ≥ 5 , BU < 5 but expected to have a high anamnestic response to FVIII or FIX, Pre- and Post-treatment Bethesda titer, BU < 5 but expected to be refractory to increased dosing of FVIII or FIX, Pre- and Post-infusion factor levels), previous immune tolerance induction (ITI) therapy.

A disease history listing will also be created.

7.6.3 Surgery Characteristics

Surgery characteristics will be summarized by type of surgery and overall. The following characteristics will be included in the summary: predicted type (major or minor), predicted maximum blood loss in a patient without a bleeding disorder who is

undergoing this type of procedure, predicted anesthesia, actual type (major or minor), estimated actual blood loss, actual anesthesia, and surgery complications.

Listing of surgery characteristics will be created.

7.6.4 Prior Medications

Medications will be coded with World Health Organization Drug Dictionary (WHO DD) providing Anatomical Therapeutic Chemical (ATC) 2 and ATC4 codes, and PT for each medication. Number and percentage of patients taking previous bleeding medications and number and percentage of patients taking previous ITI therapy medications will be summarized by type of surgery and overall.

Previous bleeding medications and previous ITI therapy medications will be presented in 2 listings.

7.7 Efficacy Endpoints and Analysis

All the Efficacy analyses will be stratified by surgery type and overall. All analyses will then be repeated stratifying by age group (< 12 years and \geq 12 years). Efficacy population will be used for all the analyses described in this section.

7.7.1 Analysis of Primary Efficacy Endpoint

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

The proportion of “good” and “excellent” responses at 48 (\pm 4) hours will be summarized. Clopper-Pearson exact 95% confidence interval for proportion will be calculated for each surgery type and age group and overall. The summaries will include missing assessments in percent calculation, while they will still be discarded when calculating the proportion of successes and the confidence interval (CI). The missing values imputed as per section 7.3 of this SAP will be analyzed as imputed.

7.7.2 Analysis of Secondary Efficacy Endpoints

The following endpoints are considered secondary for this study:

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

The first four secondary endpoints will be analyzed similarly to the primary endpoint: numbers and percentages of successes will be summarized at each timepoint, together with their Clopper-Pearson exact confidence limits.

Difference between the expected and actual blood loss will be calculated for each surgery in the study and then summarized together with 95% confidence limits. Number of events requiring transfusion, Number of bleeding episodes (by type) at the surgical site between start of procedure and 48 (±4) hours, and Number of surgical interventions/re-explorations for bleeding episodes between start of procedure and 48 (±4) hours after last administration of LR769 will be analyzed similarly.

Hemoglobin levels will be summarized at baseline and at 48 (±4) hours after last administration of LR769. Changes from baseline will also be summarized for 48 (±4) hours timepoint. 95% confidence limits for the changes will be displayed.

Total amount of study drug administered per surgery will be summarized. A summary will be created for total amount administered per surgery, total amount administered in the hospital, and total Amount administered at home. Additionally, a separate summary will be created for total amount administered by indication.

Data listings of postoperative response assessments, transfusions, surgical interventions or invasive procedures, and bleeding episodes will be created.

7.8 Exposure and Safety Endpoints and Analysis

All the analyses in this section will be stratified by surgery type and overall, and then by age group (< 12 years and ≥ 12 years). The Safety population will be used for all the analyses described in this section.

7.8.1 Exposure to Study Treatment

The exposure analysis is a part of the secondary efficacy endpoint analysis in this study (Section 7.7.2). Tables described in this section will be generated in addition to the ones specified in section 7.7.2.

The total amount of study drug taken by patient (µg/kg and total mass [mg]), total duration of treatment (days), and the number of administrations per patient will be summarized.

A data listing of exposure to LR769 will be created.

7.8.2 Adverse Events

All AEs will be coded using MedDRA (Version 15.0). An AE will be considered a treatment-emergent adverse event (TEAE) if it occurred or worsened after the first dose of study drug. In case a patient undergoes multiple procedures in the study, the TEAE will be assigned to the latest procedure prior to the event itself. Non-TEAEs are AEs occurring after signing Informed Consent but before the first administration of study drug. TEAEs will be summarized for the Safety Population. Non-TEAEs will be summarized for all enrolled patients.

The number and percentage of patients as well as the number of events will be summarized for any TEAEs, any treatment emergent SAEs, any treatment-related TEAEs, any non-treatment-related TEAEs, any TEAEs leading to discontinuation from the study, any TEAEs leading to study drug withdrawal and any TEAEs resulting in death. Summaries will be done stratifying by SOC and PT. 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. Additionally, a summary of TEAE's by SOC, PT, and severity grade will be created.

Separate summaries and listings will be provided for treatment-emergent thromboembolic events and allergic and anaphylactic reactions.

A data listing of TEAEs will be produced. Separate listings will also be prepared for SAEs, AEs leading to death, TEAEs leading to discontinuation from the study, TEAEs

leading to study drug withdrawal, thromboembolic AEs, and allergic and anaphylactic AEs. A listing of deaths will be provided as well, including information about the primary reason for death.

7.8.3 Laboratory Data

For Hematology and Serum Chemistry, descriptive statistics of actual values and change from baseline for each laboratory parameter will be presented by timepoint and surgery type. Analyses will be performed based on the Safety Population. Data will then be categorized into the following status categories using the laboratory reference ranges: low (below lower limit of normal), normal, and high (above upper limit of normal). Shift tables summarizing changes in status from baseline to each post-baseline timepoint will be presented.

Serology and Coagulation are only collected at screening. These results will be summarized descriptively including percentage of normal/abnormal values for coagulation and percentage of positive/negative/not done for serology. For coagulation, separate summaries will be created for Local and Central laboratory results.

For urinalysis, the percentage of normal, abnormal and not clinically significant, abnormal and clinically significant, and not done will be summarized by timepoint and surgery type.

Data listings will be produced for all collected laboratory data including hematology, serum chemistry, coagulation serology, and urinalysis. Laboratory values outside the laboratory's normal ranges will be flagged as H (high, above normal) or L (low, below normal) in laboratory data listings.

7.8.4 Vital Signs and Other Safety Parameters

Descriptive statistics for the actual value at each timepoint and the change from baseline to each post baseline timepoint in SBP and DBP, heart rate, respiratory rate, and body temperature will be summarized by surgery type and overall. Analyses will be performed based on the Safety Population.

A data listing for vital signs (including body weight) will be produced.

Physical examination findings results will be summarized by percentage of normal/abnormal findings at each timepoint by surgery type and overall for the Safety Population.

Body weight will be summarized descriptively at each timepoint by surgery type and overall for the Safety Population.

Data listings will be created for Physical Examination and ECG.

7.9 Other Endpoints and Analysis

All the analyses in this section will be stratified by surgery type and overall. The Safety Population will be used for all the analyses described in this section.

7.9.1 Immunogenicity

Immunogenicity results (anti-LR769 antibodies and anti-host related impurities antibodies) will be analyzed descriptively by timepoint and surgery type for the Safety Population. No statistical hypothesis testing will be performed.

A data listing of immunogenicity data will be created.

7.9.2 Concomitant Medications

Concomitant medications will be coded with WHO DD providing ATC2 and ATC4 codes, and PT for each medication. A medication will be considered concomitant if it has started during the treatment period, or if it has started prior to the first treatment and ended within the treatment period. The number and percentage of patients taking concomitant medications will be summarized by surgery type and overall and by ATC codes for the Safety Population.

A data listing of concomitant medications will be provided.

8. INTERIM ANALYSIS

There are no planned interim analyses for this study.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Protocol Section 9.6 specifies that two-sided paired t-tests will be used to test whether the mean changes from baseline equal 0 for laboratory and immunogenicity data as well as for vital signs. These tests will not be performed as they are deemed unnecessary.

10. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the protocol number will be presented. On the next line a table/listing number followed by the title of the table/listing and population information will be displayed. A blank horizontal line will appear after the column headings of the table/listing. Footnotes will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The SAS program name will appear bottom left in a string and the page number will appear on the bottom right corner of each table/listing. The date and time of creation of table/listing will appear bottom left under the SAS program name line.

Courier New 8-point bold font will be used for all tables and listings. Landscape layout will be used for both tables and listings, SAS page settings linesize=137 and pagesize=47 will be used. Any date information in the listing will use the date9. format, for example, 07MAY2002.

All outputs will be provided in the PDF (text) and in the RTF (columnar) formats.

The International Council for Harmonisation (ICH) numbering will be used for all tables, figures and data listings.

Missing values for both numeric and character variables will be presented as blanks in data listings. In tables, a zero (0) may be used if appropriate to identify when the frequency of non-missing observations for a variable is 0.

All observed time values will be presented using a 24-hour clock HH:MM format (e.g. 15:26).

Time durations will be reported in HH:MM notation. The use of decimal notation to present (display) time durations should be avoided (e.g. 0.083h = 5m) unless it is necessary to show the computation of time differences in a table, figure, or data listing, in which case both notations may be used to display the time duration.

11. TABLES, LISTINGS, AND FIGURES

A detailed list of tables, figures and listings (TFLs) is prepared and maintained as a separate document – TFL shells.

12. 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
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