COVER PAGE

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

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LFB USA Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL LFB-FVIIa-007-14

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

Protocol code:	LFB-FVIIa-007-14
Drug product code:	Coagulation Factor VIIa (Recombinant), LR769
SAP Version:	Final 2.0
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Author:	[redacted]

DOCUMENT HISTORY

Final version 1 approved: 11Jul2016

Final version 2 approved: 12Sep2017

CHANGE LOG

SAP Section Affected	Description:
5 and 7.7.2	Wording in the secondary endpoint #2 and #3 and tertiary endpoints #1, #3 and #4 definitions has been changed from “mild/moderate and severe separately and combined” to “mild/moderate only and mild/moderate and severe combined” *Reason*: text modified to reflect analysis intent.
5 and 7.7.3	New Tertiary Endpoint – VAS Pain score has been added *Reason*: text modified to reflect analysis intent.
5 and 7.7.3	Wording in the tertiary endpoint #2 definition has been changed from “within 24 hours” to “up to 24 hours” *Reason*: text modified to reflect analysis intent.
7	All sections describing allocation of safety endpoints to treatment arm have been changed. Previous approach of assigning according to the “last dose of the study drug received prior to assessment” has been replaced with “last dose regimen used prior to the assessment”. *Reason*: New approach is deemed more appropriate and consistent by the sponsor.
7.1	Wording has been changed to indicate that not all analyses will be repeated stratifying by age group. *Reason*: To keep the section consistent with changes in section 7.6.
7.1	Following wording has been added to the section: “As appropriate, additional analyses may be conducted, using different thresholds for the stratification.” *Reason*: To allow for additional subgroup analyses using different age thresholds.

7.6	Analyses stratified by age group have been removed. *Reason*: The analyses in question are unnecessary. They may be included in the addendum analysis if deemed necessary.
7.7.3	Definition of pain relief endpoint has been changed. The old algorithm stipulated a change lower than -11 to be necessary for pain relief, while according to the new algorithm any decrease in the pain is sufficient. *Reason*: To keep it consistent with the definition from PERSEPT1 study.
7.9.3	Definition of Concomitant Medication has been added. *Reason*: to add more clarity to the analysis description.
8	Interim analysis section has been expanded to include detailed description of the efficacy endpoint review performed during the interim analysis. Description of Dry Run analyses has also been added. *Reason*: to add more clarity to the analysis description
9	The section has been updated to describe the inclusion of new tertiary endpoint as well as the change in wording for the secondary and tertiary endpoints *Reason:* this was a necessary update of the definition of endpoints vs what was originally presented in the study protocol (Amendment 4.0).

APPROVAL 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

PROTOCOL NUMBER: LFB-FVIIa-007-14 Amendment 4 29 June 2016

SAP Final 2.0, 12SEP2017

[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase (SGPT)
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase (SGOT)
ATC	Anatomical Therapeutic Chemical
BU	Bethesda Units
BUN	Blood Urea Nitrogen
CHDR	Centre for Human Drug Research
CI	Confidence Interval
CSR	Clinical Study Report
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
FIX	Factor IX
FVII(a), FVIIa	Factor VII activated
GBS	Good Biomarker Sciences
GGT	Gamma Glutamyl Transferase
Hct	Hematocrit
HEENT	Head, Eyes, Ears, Nose, Throat
Hgb	Hemoglobin
ICH	International Conference on Harmonisation
ITI	Immune Tolerance Induction
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
OPC	Objective Performance Criterion
PK	Pharmacokinetic
PT	Preferred Term
Q1	First quartile

Q3	Third quartile
RBC	Red Blood Cell (count)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
SOC	System Organ Class
TAAE	Treatment Associated Adverse Event
TEAE	Treatment Emergent Adverse Event
VAS	Visual Analog Scale
WBC	White Blood Cell (count)
WHO DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) covers the statistical analysis and reporting for the protocol LFB-FVIIa-007-14 version 4.0 dated 29 Jun 2016, and eCRF dated 07 October 2015.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- 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

- 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

2.3 Other Objectives

- 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. STUDY DESCRIPTION

3.1 Study Design

This is a global, multicenter, Phase III, Prospective, Open-label, Randomized, Crossover Study. There are two patient age ranges (from birth to less than 6 years and 6 years to less than 12 years); at least 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 initial safety and PK phase, Phase A, and the dose to be used when starting the treatment phase, Phase B, before crossover to the other treatment regimen.

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 adverse event (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 of the protocol 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 number 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 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 dose 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 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 later with 75 µg/kg every 3 hours until the bleeding episode is successfully treated. A maximum of 6 treatments in total within a 21-hour period are allowed in this treatment regimen for mild/moderate bleeding episodes.

If the bleeding episode was not successfully treated as assessed at 24 hours after the first administration, treatment with LR769 should 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 (e.g., FEIBA® or NovoSeven®) 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.

3.1.2.2 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 (e.g., FEIBA® or NovoSeven®) or any other hemostatic treatment effective for inhibitor patients

3.2 Study Treatment

After obtaining informed consent of the parent/guardian 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 initial safety and PK phase, Phase A, and is the dose to be used when starting the treatment phase, Phase B, before crossover to the other treatment regimen.

3.3 Data Monitoring Committee (DMC)

The DMC will convene to review safety data. Details will be documented in a separate DMC charter.

4. SAMPLE SIZE AND POWER CALCULATION

The proportion 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 successfully treated. (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 mild/moderate bleeding episodes per treatment regimen per patient) will provide statistical power ≥80%. The study will enroll at least 24 patients to account for dropouts and potential unevaluable bleeding episodes.

5. ANALYSIS ENDPOINTS

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 may 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

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) or 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.

Secondary Efficacy Endpoints

• 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 only and mild/moderate and severe 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 only and mild/moderate and severe 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

Tertiary Efficacy Endpoints

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe 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 up to 24 hours after an initial successful response)

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe combined) requiring alternative treatment

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe combined) with successful pain relief

• VAS Pain score values at all timepoints for mild/moderate and severe bleeding episodes, analyzed separately and combined

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 Endpoints

Pharmacokinetic (PK) endpoints include plasma FVIIa concentrations (as measured by activity assay) at each timepoint and PK parameters. A separate pharmacokinetic analysis plan (PKAP) has been written prior to performing the analyses.

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.

6. ANALYSIS POPULATIONS

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

The Safety Population will be defined as all enrolled patients who received at least one dose of study treatment (either in Phase A and/or Phase B). All safety endpoints and baseline characteristics will be analyzed on this population.

The Treated Population will be defined as all enrolled patients who received at least one administration of study drug to treat a bleeding episode during Phase B. All analyses of efficacy will be performed based on the Treated Population. At a bleeding-episode level, the analysis will include all bleeding episodes treated with study drug, and each such bleeding episode will be analyzed as treated.

The Evaluable PK Population will be defined as all treated patients who have post study drug administration factor VIIa activity levels. All PK analyses will be based on this population. A separate pharmacokinetic analysis plan (PKAP) will be written prior to performing the analyses.

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, median, Q1, Q3, and minimum and maximum values. All raw data will be presented to the original number of decimal places. Means, medians, Q1, and 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.

All summary statistics will be reported stratifying by treatment regimen and overall. Two different approaches to treatment stratification will be used:

- The Baseline characteristics will be analyzed by treatment arm assigned at randomization
- Efficacy and Safety endpoints will be analyzed according to the treatment arm used to treat the particular bleeding episode

Additionally, analyses will be repeated further stratifying by age group (birth to <6 years and ≥6 years to <12 years) when applicable. As appropriate, additional analyses may be conducted, using different thresholds for the stratification.

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. All analyses will use the visits as reported in the eCRF. No reassignment of the visits will be done. However, timepoints of bleeding episode efficacy assessments and additional injections will be reassigned in accordance with the time passed since the first study drug injection for a given bleeding episode. The timepoints will be assigned according to the schedule, depending on the severity of the bleeding episode and the drug regimen used. A lag of 30 minutes will be allowed for (so, any assessment/injection that happened between 11 hours 30 minutes and 12 hours 29 minutes after the first administration of the study drug will be assigned to “12 Hours” timepoint).

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.

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 “15JULYYYY”. In case of missing day the date will be replaced with “01MMMYYYY”.

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 less than Year for the First Treatment Date, then impute July 15th of the year.
- If Day and Month are missing for Start Date and the Year is greater than Year for the First Treatment Date, then impute January 1st of the year.

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.

Three ways of imputation of missing data for the primary efficacy endpoint will be used as sensitivity analyses and are discussed in the Analysis of Primary Efficacy Endpoint section of this SAP.

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. No stratification by treatment regimen will be implemented for this analysis.

The number of enrolled patients will be summarized along with the number and percentage of enrolled patients in the Safety, Treated and Evaluable PK Populations completing the study, withdrawing from the study and the primary reason for withdrawal, and the number of deaths, stratifying by planned treatment regimen and overall.

Data listings of patient disposition, screen failures, and patient assignment to analysis groups will be created.

7.5 Protocol Deviations

Deviations from the protocol will be recorded in the EDC and reviewed on a monthly basis by Medical Monitors. Protocol deviations and corresponding categories are defined in the Medical Monitoring Plan, including identification, classification (major/minor), and as well as their consequence for the inclusion in the different analysis populations. A data 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 randomized initial treatment regimen and overall for the Safety Population, and Treated Population. Demography data will be additionally summarized for PK Evaluable population. The following parameters will be summarized:

- Age at informed consent
- Race
- Ethnicity
- Sex

- Weight at baseline
- Height at baseline
- BMI at baseline
- Vital Signs (SBP, DBP, Heart rate, etc.) at baseline
- Physical Examination at baseline

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

A data listing of baseline and demographic characteristics will be created.

7.6.2 Medical History and Concurrent Medical Conditions

Medical history will be summarized by randomized treatment regimen and overall for Safety and Treated populations. The number of patients with prior and concurrent conditions for the following medical condition categories will be summarized: Any Medical History or Current Medical Conditions, Infectious Diseases, Allergies, Metabolic/Endocrine/Nutritional, Hematopoietic, Musculoskeletal, Dermatologic, HEENT, Breasts, Respiratory, Cardiovascular, Gastrointestinal/Hepatic, Genitourinary/Renal, Neurologic, Psychiatric/Psychosocial, and Other.

A data listing of prior and concurrent medical conditions will be created.

Disease history data will also be summarized by planned treatment regimen and overall for Safety and Treated populations. The following parameters will be included in the summary: type of hemophilia, hemophilia severity grade at screening, factor, factor level (%), Inhibitor status (Bethesda units [BU] ≥5, BU < 5, BU <5 but expected to have a high anamnestic response to FVIII or FIX, BU <5 but expected to be refractory to increased dosing of FVIII or FIX), number of bleeding episodes during the past 6 months prior to entry in the study, whether the patient has a target joint(s)/bleeding site(s), Immune Tolerance Induction (ITI) therapy past, ITI therapy present.

A data listing of disease history will be created.

7.6.3 Prior Medications

Medications will be coded with World Health Organization Drug Dictionary (WHO DD Mar 2015) providing ATC2 and ATC4 codes, and preferred term (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 planned treatment regimen and overall and by Anatomical Therapeutic Chemical (ATC) codes for Safety and Treated populations.

Data listings for previous bleeding medications and previous ITI therapy medications will be created.

7.6.4 Characteristics of Bleeding Episodes

The following characteristics of bleeding episodes (obtained from the eCRF and from Patient Diaries) will be summarized by treatment regimen used to treat the episode and overall:

- Location of bleeding
- Target joint/bleeding site
- Severity
- Cause
- Recurrences
- Was a visit to hospital necessary?
- Was alternative treatment used?
- Total and per-patient number of bleeding episodes treated
- Time between start and of bleeding episode and treatment
- Number of administrations per bleeding episode
- Total Dose per Bleeding Episode

This will be done separately for mild/moderate and severe bleeding episodes, and for all bleeding episodes, regardless of severity.

A data listing of bleeding episode characteristics will be created.

7.7 Efficacy Endpoints and Analysis

All the Efficacy analyses will be run for all patients in the Treated Population and stratified by age group.

7.7.1 Analysis of 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. Detailed definition of the endpoint can be found in Section 5 of this document.

For each LR769 treatment regimen, the observed proportion ($\hat{p}$) of successful treatment of a bleeding episode at 12 hours after first administration of the study drug will be summarized using the count and percentage. A 95% normal approximation confidence interval (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: $p > 0.55$

where p is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours.

The null hypothesis will be tested using a 1-sided, 1-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 (see below for the details). 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 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.

To account for the correlation between bleeding episodes from the same patient, the test statistic will be computed as follows:

$$Z = \frac{\hat{p} - 0.55}{\hat{\sigma}(\hat{p})},$$

where

$$\hat{p} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} x_{i,j}}{\sum_{i=1}^{n} m_i},$$

with $x_{i,j}$ = result for jth episode for ith subject, j=1,2,..., m_i; i=1,2,...,n.

= 1 if the bleeding episode is a success

= 0 otherwise,

where n = the number of patients and m_i = the number of episodes for the i^{th} patient.

$$\hat{\sigma}(\hat{p}) = \left\{ \frac{\hat{p}(1-\hat{p})\sum_{i=1}^{n}\{m_i[1+(m_i-1)\hat{\rho}]\}}{(\sum_{i=1}^{n} m_i)^2} \right\}^{1/2},$$

$$\hat{\rho} = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i}\sum_{j'=1, j\neq j'}^{m_i}(x_{i,j}-\bar{x})(x_{i,j'}-\bar{x})}{\sum_{i=1}^{n}(m_i-1)\sum_{j=1}^{m_i}(x_{i,j}-\bar{x})^2},$$

$$\bar{x} = \frac{\sum_{i=1}^{n}(m_i - 1)\sum_{j=1}^{m_i} x_{i,j}}{\sum_{i=1}^{n} m_i(m_i - 1)}.$$

A table summarizing the results of the primary efficacy analysis (described above) of primary efficacy endpoint will include the number of patients, number of mild/moderate bleeding episodes, number of bleeding episodes successfully treated, number of failures, and number of missing values, stratified by actual treatment regimen and overall. The sample proportion of successes will be presented as well, together with a 95% CI for the true proportion and the p-value for the test of H_0, comparing the sample proportion with 0.55. The test will be conducted for both treatment regimens separately and overall. The table will be created for Treated Population.

No imputation of missing data will be performed for the primary analysis of primary efficacy endpoint. However, 3 sensitivity analyses will be performed 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. Additionally, if the primary efficacy analysis concludes that the true proportion of successes is greater than 0.55 and, at the same time, this result is lost in the first sensitivity analysis, a third sensitivity analysis will be performed. The purpose of this third analysis will be to determine the number and proportion of missing values that have to be assigned as failures (“tipping point”) to make the effect observed in the primary analysis non significant.

Success proportions will be compared between the two LR769 treatment doses using a 2-sided, normal approximation test, taking into account the correlation between bleeding episodes receiving the same treatment for a given patient and also the correlation between bleeding episodes receiving different treatments for a given patient, with an alpha of 0.05. A table summarizing the proportion of successfully treated bleeding episodes by actual treatment regimen and overall, as well as the p-value from the test, will be created. The test statistic is defined as follows:

$$Z = \frac{\hat{p}_1 - \hat{p}_2}{\hat{\sigma}(\hat{p}_1 - \hat{p}_2)}$$

$$\hat{p}_1 = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i} X_{i,j}}{\sum_{i=1}^{n} m_i} \quad \text{and} \quad \hat{p}_2 = \frac{\sum_{i=1}^{n}\sum_{j=1}^{l_i} Y_{i,j}}{\sum_{i=1}^{n} l_i}$$

$$\hat{\sigma}(\hat{p}_1 - \hat{p}_2) = [\frac{\hat{p}_1(1-\hat{p}_1)\sum_{i=1}^{n}\{m_i[1+(m_i-1)\hat{\rho}_1]\}}{(\sum_{i=1}^{n} m_i)^2}$$

$$+ \frac{\hat{p}_2(1-\hat{p}_2)\sum_{i=1}^{n}\{l_i[1+(l_i-1)\hat{\rho}_2]\}}{(\sum_{i=1}^{n} l_i)^2} - 2(\frac{\hat{\rho}_3[\hat{p}_1(1-\hat{p}_1)\hat{p}_2(1-\hat{p}_2)]^{1/2}}{\sum_{i=1}^{n} m_i \sum_{i=1}^{n} l_i})\sum_{i=1}^{n} m_i l_i]^{1/2}$$

and

$$\hat{\rho}_1 = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i}\sum_{j'=1}^{m_i}(x_{i,j}-\bar{x})(x_{i,j'}-\bar{x})}{\sum_{i=1}^{n}(m_i-1)\sum_{j=1}^{m_i}(x_{i,j}-\bar{x})^2}, \text{ where } \bar{x} = \frac{\sum_{i=1}^{n}(m_i-1)\sum_{j=1}^{m_i} x_{i,j}}{\sum_{i=1}^{n} m_i(m_i-1)},$$

$\hat{\rho}_2$ is defined similarly based on the y observations, and

$\hat{\rho}_3$, the sample estimate of ρ_3, is the Pearson sample correlation coefficient calculated using all ordered pairs of observations $(x_{i,j}, y_{i,j'})$, $i = 1,2,...,n$; $j = 1,2,..., m_i$; $j' = 1,2,..., l_i$.

Two additional 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-patient correlation. The model will include the term for treatment as the only fixed effect.

Analyses described above will be performed for both definitions of the primary efficacy endpoint (for the FDA and the EMA). For the EMA definition of the primary endpoint additional analysis will be conducted, summarizing the success for severe bleeding episodes only.

A data listing of treatment of all mild/moderate bleeding episodes will be created. Additionally, a separate data listing of treatment of severe bleeding episodes will be created.

7.7.2 Analysis of Secondary Efficacy Endpoints

The following endpoints are considered secondary for this study:

• Proportion of mild/moderate bleeding episodes successfully treated according to the same criteria as the primary endpoint as per definition for the FDA of efficacy, at all other timepoints

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe 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 only and mild/moderate and severe 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

The first and second secondary efficacy endpoints listed above will be analyzed similarly to the primary efficacy endpoints (section 7.7.1), except that no sensitivity analyses and no generalized estimating equations analysis nor generalized linear mixed models analysis will be performed. The number of administrations of study drug per bleeding episode and the total amount of study drug administered per bleeding episode will be summarized descriptively on a bleeding episode level by actual treatment regimen used for a bleeding episode and overall using descriptive statistics. No inferential statistical analyses will be performed for these endpoints.

The time to patient assessment of a “good” or “excellent” response of the bleeding episodes 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.

The rules for censoring will be similar for all time-to-event endpoints, regardless of what assessor and what type of bleeding episode is analyzed. If a “good” or “excellent”

response was reported for a bleeding episode, it will be considered an event, with time to event equal to the time from start of treatment to reporting a "good" or "excellent" response. If a rescue treatment was received for a bleeding episode at any time prior to a "good" or "excellent" response, the bleeding episode will be considered a failure and will be assigned a censored value at the final timepoint. Bleeding episodes that do not achieve a “good” or “excellent” response by the patient will be censored at the time of last response.

Summaries for the number of administrations of study drug and total amount of study drug administered will be created for mild/moderate bleeding episodes and then repeated for all bleeding episodes.

7.7.3 Analysis of Tertiary Efficacy Endpoints

The following endpoints are considered tertiary:

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe 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 up to 24 hours after an initial successful response

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe combined) requiring alternative treatment

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe combined) with successful pain relief (a negative change from baseline in Visual Analog Scale [VAS] pain-score at 12 hours)

• VAS Pain score values at all timepoints for mild/moderate and severe bleeding episodes, analyzed separately and combined

All of these endpoints will be analyzed using the same approach as described in Section 7.7.1 for the proportion of successfully treated bleeding episodes at 12 hours, except that no sensitivity analyses, no comparison with OPC, and no GEE logistic regression and GLMM analyses will be performed. Also, no subgroup analysis for different age groups will be performed for tertiary endpoints.

VAS pain scores of mild/moderate bleeding episodes and severe bleeding episodes separately and combined will be summarized at the bleeding episode level by actual treatment regimen and overall by timepoint using descriptive statistics.

7.8 Exposure and Safety Endpoints and Analysis

All analyses in this section will be performed overall and separately for two age groups.

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 (months), and the number of administrations of each dose by patient will be summarized for the Safety and Treated populations.

Separate data listings for treatment of mild/moderate and of severe bleeding episodes will be created. Additionally, a data listing of Phase A PK administrations will be created. Data listings of Study Interruptions and Surgical/Therapeutical Procedures will also be created.

7.8.2 Adverse Events

All AEs will be coded using the Medical Dictionary of Regulatory Activities (MedDRA 15.0). An AE will be considered treatment emergent (TEAE) if it occurred or worsened after the first dose of study drug. 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 (and serious non TEAEs) will be summarized for all Enrolled patients. TEAEs will be assigned to the most recent treatment regimen received by the patient prior to the onset of the AE. TEAEs and non-TEAEs will be summarized by system organ class (SOC) and preferred term (PT).

Treatment-associated AEs (TAAE) will be summarized by SOC and PT for the Safety Population. An AE will be considered a TAAE if it occurs between the start of treatment of a bleeding episode (or study drug administration for PK purposes, outside a bleeding episode) and the end of treatment of the bleeding episode, up to and including the 24 hours after the last administration of study drug for that bleeding episode (or administration for PK purposes). Thus, AEs that occur in between the treatments of two bleeding episodes will not be considered TAAEs.

The number and percentage of patients with any TEAEs, any TAAEs, any serious TEAEs (SAEs), any treatment-related TEAEs, any TEAEs leading to withdrawal from the study, any TEAEs leading to discontinuation of study drug, and any TEAEs resulting in death will be presented for all patients by treatment regimen and overall for Phases A and B separately, as well as for both phases combined. Summaries will also include the number of events observed in each category and a ratio between the number of events and the number of treatment administrations with a given treatment regimen. 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.

TEAEs and non TEAEs will also be summarized by worst severity. Separate data listings of TEAEs , TAAEs, and non TEAEs will be created. Separate data listings will also be prepared for SAEs and AEs leading to death. A listing of deaths will be provided as well, including information about the primary reason for death.

All the AE-related outputs will be reported overall and separately for age groups.

7.8.3 Laboratory Data

No local laboratory data will be collected in this study – all samples will be analyzed by central laboratory. Laboratory parameters for the following categories will be summarized: hematology, serum chemistry, and coagulation. Descriptive statistics of actual values and change from baseline for each laboratory parameter will be presented by visit. Analyses will be performed based on the Safety Population (actual treatment regimen and overall). Similarly to AE analysis, the assessment will be assigned to a dose level according to the last treatment regimen taken prior to the assessment. No hypothesis testing will be performed. All laboratory data will 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 visit will be presented.

Immunogenicity data will be summarized by visit. Counts and percentages of positive and negative results will be presented for both screening and confirmatory assays.

All of the lab test analyses will also be performed by age group.

Data listings will be created for all collected laboratory data including hematology, chemistry, and coagulation. Laboratory values outside laboratory's normal ranges will be flagged as H (high, above normal) or L (low, below normal) in laboratory data listings. Listing of Immunogenicity data will also be prepared.

7.8.4 Vital Signs and Other Safety Parameters

Descriptive statistics of actual value and the change from baseline for each vital sign parameter (systolic and diastolic BP, heart rate, respiratory rate, and body temperature) will be presented by visit. The assessment will be assigned to a dose level according to the last treatment regimen taken prior to the assessment. . Analyses will be performed based on the Safety Population. Vital sign analyses will also be performed by age group.

A data listing for vital signs and weight will also be created.

Physical examination findings will be summarized at each timepoint using counts and percentages of normal and abnormal findings, stratifying by actual treatment regimen at Baseline and overall for the Safety Population.

A data listings will be created for physical examination findings.

7.9 Other Endpoints and Analysis

7.9.1 Pharmacokinetics

The PK analysis will be done separately from the main analysis by Good Biomarker Sciences (GBS) and the sponsor. The PK SAP will be drafted and will contain a detailed description of the PK analysis. A separate PK report will summarize the results.

7.9.2 Healthcare Resource Utilization

The number of days lost from work or school due to bleeding or complications of bleeding, the number of non study visits to the hospital/hemophilia treatment center, the number of days of inpatient hospitalization, and the number of days away from school or work (if applicable) for patient and parent/legal guardian due to bleeding episodes will be summarized by planned treatment regimen at baseline and overall. Analyses will be performed based on the Treated Population.

A data listing for healthcare resource utilization will be created.

7.9.3 Concomitant Medications

Concomitant medications will be coded with WHO DD Mar 2015 providing ATC2 and ATC4 codes, and preferred term for each medication. A medication will be considered concomitant if it has started during the treatment period, or if it has started prior ti the first treatment and ended within the treatment period. The number and percentage of patients taking concomitant medications will be summarized by planned treatment regimen at baseline and overall and by ATC codes for the Safety Population. Concomitant medication data will also be analyzed separately by age group.

A data listing of concomitant medications will be created.

Separate summary tables and a data listing will be created for concomitant bypassing agents (FEIBA or Novo7).

8. INTERIM ANALYSIS

One formal interim analysis will be performed once both below conditions are satisfied:

- Upon availability of FVIIa plasma activity data for at least 6 patients in each age group, PK profiles along with all relevant 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.

A full list and shells for the outputs to be provided can be found in the DMC Charter version 2.0 dated 25 September 2015.

Efficacy Endpoint Review

Individual mild and moderate bleeds will be reviewed for accuracy and consistency based on the following:

- Timing of each bleeding episode, associated dose and efficacy assessments, including the completeness of values to isolate missing values
- Dosing details relative to efficacy assessments (e.g., ensuring that patient was not dosed after a good or excellent response)
- Protocol deviations associated with each bleeding episode
- Associated concomitant medications to ensure that no hemophilia treatments were given during a bleeding episode (for example, Novo 7, Feiba, blood transfusions)
- Confirmation whether a bleeding episode was successfully treated or not.

Dry Run Review

Dry run review of data will be conducted by the Clinical Study Team. The main purposes of this review are: 1) to identify any data issues that need to be resolved; 2) to identify any programming issues; and 3) to confirm completeness of the TLFs for reporting purposes.

A select group of individuals will look into dry run results to recommend additional analyses that will be included in the clinical study report. These potential analyses will be included in a separate SAP addendum document. The SAP addendum document will be finalized before database lock but implementation will occur post-database lock.

Final analyses will commence after all subjects have completed their final visit and as soon as the database is confirmed cleaned and locked. These analyses will be performed in accordance to the methodology stipulated in this SAP.

9. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

Definitions of the secondary efficacy endpoints #2 and #3 and tertiary endpoints #1, #2, #3 and #4 have been altered from the protocol, to better reflect the planned analysis. Wording has been changed from “mild/moderate and severe separately and combined” to “mild/moderate only and mild/moderate and severe combined”.

New tertiary endpoint “VAS Pain Score at different timepoints” has been added to reflect the intended analysis.

There are no other deviations from analysis as planned in the Protocol.

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. Each table/listing/figure will be output in an individual file.

The International Council for Harmonisation (ICH) numbering.

Missing values for both numeric and character variables will be presented as blanks in data listings. In case of imputation of data, the imputed data will be presented in the listings and flagged. 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 is prepared and maintained as a separate document – TFL shells.

12. BIBLIOGRAPHY

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

Chen YH, DeMets DL, Lan KK (2004) Increasing the sample size when the unblinded interim result is promising. Stat Med 23:1023-1038

Dubois A, Gsteiger S, Pigeolet E, Mentre F (2010) Bioequivalence tests based on individual estimates using non-compartmental or model-based analyses: evaluation of estimates of sample means and type I error for different designs. Pharm Res 27:92-104

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

Lachin JM (2005) A review of methods for futility stopping based on conditional power. Stat Med 24:2747-2764

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

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

Valentino LA CD (2009) Hemophilia and Thrombosis Research Society (HTRS) Registry data to understand differences in recombinant factor VIIa (rFVIIa) dosing and clinical outcomes for the treatment of specific joint bleeds in hemophilia. Journal of Thrombosis and Haemostasis 7, Suppl. 2:Abstract PP-TH-602

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