# 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 (v2.0) ADDENDUM

## 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 |
| **Addendum SAP Version:** | Final 1.0 Addendum to SAP v2.0 |
| **Creation Date:** | 25 September 2017 |
| **Author:** | [redacted] |

# 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

Addendum to SAP version 02, 12SEP2017

[redacted]

# 1. INTRODUCTION

This document covers additional analyses to be performed for the protocol LFB-FVIIa-007-14 version 4.0 dated 29 Jun 2016, eCRF dated 07 October 2016, and is considered as an addendum to the main SAP version 2.0 dated 12 September 2017 and Mock TFL's version 2.0 dated 12 September 2017. Due to timelines and planning considerations, the below analyses are intended to be executed post-database lock.

# 2. ANALYSIS DESCRIPTION

Tables and figures specified in this document will be reported separately from the main output and marked explicitly as addendum tables (see the example in section 3 of this document).

Analyses of the primary efficacy endpoint (Tables 14.2.1.1 through 14.2.2.3 of the main analysis) will be re-run stratifying by age group, using the following strata: <2 years, 2 to <6 years and 6 to <12 years. The same analyses will then be repeated stratifying by BMI, categorized into three classes by tertiles.

Additionally, GEE and GLMM models for primary endpoint will be re-run with PK parameters (e.g., AUClast, AUCinf, and Cmax), BMI and age group as covariates (see Table 14.2.3.1 as a reference).

The following secondary and tertiary efficacy endpoints will be analyzed stratifying by age groups and BMI using the same categories above.

• Proportion of mild/moderate bleeding episodes successfully treated according to the same criteria as the primary endpoint as per the FDA definition of efficacy, at all other timepoints (see Table 14.2.4.1.1 as reference)

• 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 (see Tables 14.2.4.3.1 and 14.2.4.4.1 as reference)

• 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) (see Tables 14.2.5.1.1 and 14.2.5.2.1 as reference)

• Proportion of bleeding episodes (mild/moderate only and mild/moderate and severe combined) with a "good" or "excellent" physician reported assessment of efficacy at 12 hours (if available) (see Tables 14.2.4.6 and 14.2.4.7 as reference)

• Proportion of recurrences (defined as a bleeding in the same joint/anatomical location within 24 hours after an initial successful response (see Tables 14.2.7.1.1 and 14.2.7.1.2 of the main output as reference)

Time plots for the following parameters will be created, splitting the data by age group (<2 years, 2 to <6 years and 6 to <12 years) and study drug dose:

- 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 primary efficacy endpoint)
- Proportion of bleeding episodes (mild/moderate and severe, analyzed separately and combined) with a “good” or “excellent” patient (and/or physician when available) reported assessment of efficacy
- Proportion of bleeding episodes still ongoing

The time reported on the plots defined above will be derived as a difference between the time of event (success or end of the bleeding episode) and the time of first study drug injection for the associated bleeding episode.

Additionally, a new analysis summarizing the number of injections required to produce a response (FDA and EMA definition analyzed separately) and time required to reach a response will be conducted. This analysis will also be re-run stratifying by age group using the same thresholds as discussed above. Mock Tables for this analysis can be found in section 3. Time required to reach a response will also be analyzed using the Kaplan-Meier model, as described in the main SAP.

# 3. SHELL TABLES FOR THE NEW ANALYSES

**Table Addendum 14.2.8.1.1 Number of Administrations of Study Drug and Time Required to Reach a Response (FDA Definition) - Mild/Moderate Bleeding Episodes (Treated Population)**

| Parameter | Statistic | 75 µg/kg (N=xx) | 225 µg/kg (N=xx) | Overall (N=xx) |
|---|---|---|---|---|
| Number of administrations of study drug required to produce a response (BEs with response only) | n | xx | xx | xx |
| | nmiss | xx | xx | xx |
| | Mean (SD) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | Median | xx | xx | xx |
| | Q1/Q3 | xx.x/xx.x | xx.x/xx.x | xx.x/xx.x |
| | Minimum/Maximum | xx/xx | xx/xx | xx/xx |
| Time required to reach a response (hours)(BEs with response only) | n | xx | xx | xx |
| | nmiss | xx | xx | xx |
| | Mean (SD) | xx (xx.x) | xx (xx.x) | xx (xx.x) |
| | Median | xx | xx | xx |
| | Q1/Q3 | xx.x/xx.x | xx.x/xx.x | xx.x/xx.x |
| | Minimum/Maximum | xx/xx | xx/xx | xx/xx |
| Kaplan-Meier Model results for Time required to reach a response (hours)(All BEs) | | | | |
| Censored Summary | | | | |
| | Bleeding Episodes with Event | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
| | Censored Bleeding Episodes | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
| | Missing | xx (xx.x%) | xx (xx.x%) | xx (xx.x%) |
| Kaplan-Meier Estimates | | | | |
| | Q1 (C.I.) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| | Median (C.I.) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |
| | Q3 (C.I.) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) | xx.x (xx.x, xx.x) |

Note: Table is stratified by actual treatment regimen at bleeding episode.

**Table Addendum 14.2.8.1.2 Number of Administrations of Study Drug and Time Required to Reach a Response (FDA Definition) - Mild/Moderate Bleeding Episodes (Treated Population) – Patients from birth to less than 2 years**

Similar to Table Addendum 14.2.8.1.1

**Table Addendum 14.2.8.1.3 Number of Administrations of Study Drug and Time Required to Reach a Response (FDA Definition) - Mild/Moderate Bleeding Episodes (Treated Population) – Patients 2 years to less than 6 years**

Similar to previous

**Table Addendum 14.2.8.1.4 Number of Administrations of Study Drug and Time Required to Reach a Response (FDA Definition) - Mild/Moderate Bleeding Episodes (Treated Population) – Patients 6 years to less than 12 years**

Similar to Table Addendum 14.2.8.1.1

**Table Addendum 14.2.8.2.1 Number of Administrations of Study Drug and Time Required to Reach a Response (EMA Definition) - Bleeding Episodes Regardless of Severity (Treated Population)**

Similar to Table Addendum 14.2.8.1.1

**Table Addendum 14.2.8.2.2 Number of Administrations of Study Drug and Time Required to Reach a Response (EMA Definition) - Bleeding Episodes Regardless of Severity (Treated Population) – Patients from birth to less than 2 years**

Similar to previous

**Table Addendum 14.2.8.2.3 Number of Administrations of Study Drug and Time Required to Reach a Response (EMA Definition) - Bleeding Episodes Regardless of Severity (Treated Population) – Patients 2 years to less than 6 years**

Similar to Table Addendum 14.2.8.1.1

**Table Addendum 14.2.8.2.4 Number of Administrations of Study Drug and Time Required to Reach a Response (EMA Definition) - Bleeding Episodes Regardless of Severity (Treated Population) – Patients 6 years to less than 12 years**

Similar to Table Addendum 14.2.8.1.1