Application Type	BLA
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Division / Office	OTAT
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	Laboratoire Francais Du Fractionnement Et Des Biotechnologies S.A. / 2061
Established Name	Coagulation Factor VIIa (Recombinant)
(Proposed) Trade Name	SevenFact™
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	Milk of transgenic rabbits which express recombinant human Factor VII. FVII protein is isolated from the milk
Dosage Form(s) and Route(s) of Administration	Intravenous
Dosing Regimen	1 mg, (b) (4) 5 mg of LR769 (glass vials)
Indication(s) and Intended Population(s)	On-demand treatment and control of bleeding episodes in adolescent and adult hemophilia A or B subjects with inhibitors

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GLOSSARY

AE	adverse event
aPTT	activated partial thromboplastin time
BSL	baseline
BU	Bethesda Unit
CL	clearance
CV	coefficient of variation

GLOSSARY

AE	adverse event
BU	Bethesda unit
DAO	data as observed
FVIII	factor VIII
FIX	factor IX
FEIBA	factor eight inhibitor bypassing agent
FVIIa	activated form of Factor VII
GEE	generalized estimating equations
ITI	immune tolerance induction
LR769	Sevenfact™ (coagulation factor VIIa [recombinant])
OPC	objective performance criterion
rFVIIa	coagulation factor VIIa [recombinant]
SAE	serious adverse event
TEAE	treatment emergent adverse event
TAAE	treatment-associated adverse event

1. EXECUTIVE SUMMARY

The investigational product LR769 (Coagulation Factor VIIa [Recombinant], rFVIIa), is a recombinant form of the naturally occurring plasma coagulation factor VII that is activated during the purification process.

The applicant submitted data from a single completed study (PERSEPT 1), a multi-regional, prospective, open-label, randomized, dose crossover trial to assess the efficacy of LR769 for at-home on-demand treatment of bleeding in subjects with congenital hemophilia A or B with inhibitors to factor VIII (FVIII) or factor IX (FIX). Twenty-seven male subjects 12 years of age and above were enrolled. The study had two treatment regimens (75 μg/kg and 225 μg/kg). The primary efficacy analysis compared the proportion of successfully treated mild/moderate bleeding episodes in each treatment regimen with a pre-specified objective performance criterion (OPC) of 55%. This OPC was chosen by the applicant taking into account the reported success rate for a study used to support registration of NovoSeven® in the US and Europe.

There were 465 mild/moderate bleeding episodes combined between the two treatment regimens. Treatment was considered to be successful for 393 (84.5%) and unsuccessful for 50 (10.8%) of these bleeding episodes. The remaining 22 (4.7%) bleeding episodes had missing values at 12 hours after initial study drug administration and were excluded from the primary efficacy analysis.

The observed percentages and 95% confidence intervals [CIs] of successfully treated mild/moderate bleeding episodes for each dose group, based on non-missing assessments, were as follows:

- 84.9% (202/238; 95% CI: 74.0%, 95.7%) for the 75 μg/kg regimen. The percentage of successful treatments was significantly higher than the OPC of 55% ($p < 0.001$) at the 1-sided 0.0125 significance level.
- 93.2% (191/205; 95% CI: 88.1%, 98.3%) for the 225 μg/kg regimen. The percentage of successful treatments was significantly higher than the OPC of 55% ($p < 0.001$) at the 1-sided 0.0125 significance level.

In addition, the observed percentage of successfully treated mild/moderate bleeding episodes for the 75 μg/kg regimen was lower than that for the 225 μg/kg regimen, with the rate of treatment failures at 12 hours approximately two times higher for the 75 μg/kg regimen than for the 225 μg/kg regimen. Ten treatments considered successes by the applicant were determined to be failures by the clinical reviewer, and 22 bleeding episodes that had missing values were treated as failures. Re-analyzing the primary endpoint data with these failures did not change the outcome of the study.

The statistical results of PERSEPT 1 appear to support its use for control of bleeding episodes in patients with congenital hemophilia A or B with inhibitors to FVIII or FIX, respectively. Of note, only two subjects with hemophilia B were included in the study, limiting direct generalizability of the data to this population. I defer to the clinical review team regarding the generalizability of data in subjects with hemophilia A with inhibitors to the population of patients with hemophilia B with inhibitors.

2. CLINICAL AND REGULATORY BACKGROUND

Insert text here

2.1 Disease or Health-Related Condition(s) Studied

Patients with hemophilia A or B have a genetic disorder leading to either reduced production or a defective form of FVIII (for Type A) or FIX (for Type B), leading to excessive bleeding episodes, often in joints or subcutaneous tissue. Life-threatening bleeding in the central nervous system or gastro-intestinal system may occur as well. Treatment of bleeding usually consists of replacement of the deficient coagulation factor. The FVIII or FIX concentrates can be used in a prophylactic manner. Preventative treatment is also given prior to surgical procedures, invasive investigations (e.g., endoscopy with biopsies), or e.g., tooth extractions. Approximately 30% of severe hemophilia A patients and 1-3% of hemophilia B patients develop alloantibodies, referred to an inhibitors, to the FVIII or FIX concentrates. In the presence of inhibitors where FVIII or FIX concentrates are not effective, treatment with the activated form of Factor VII (FVIIa) provides a way to bypass the need for FVIII or FIX and initiate clotting at a site of bleeding.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

NovoSeven®, Coagulation Factor VIIa (Recombinant), is approved in the US for the treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, among other indications. Another FVIIa-containing

bypassing agent used in subjects with congenital hemophilia A or B with inhibitors is FVIII inhibitor bypassing agent (FEIBA®), a plasma-derived activated prothrombin complex concentrate which possesses less activated FVIIa.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The pre-BLA meeting was held between the applicant and the FDA on April 25, 2016, under IND 15183/CRMTS #10181. Among clinical questions discussed were dose regimens, the ongoing pediatric study, a waiver for children from birth to 6 months of age, and using LR769 for (b) (4) .

In advance of the submission of this BLA, the applicant submitted to FDA's Office of Orphan Drug Products a request for orphan drug designation of LR769 indicated for on-demand treatment and control of bleeding in subjects with hemophilia A or B with inhibitors to FVIII and FIX. This designation has not been granted to date.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

Insert text here

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

Insert text here

5.1 Review Strategy

The applicant submitted data from a single completed study (PERSEPT 1) to support the indication pursued in this BLA. No other efficacy clinical studies were completed for this product.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

BLA 125641/0

Module 1.14	Labeling
Module 1.2	Cover Letter
Module 2.2	PERSEPT 1 Introduction
Module 2.5	Clinical Overview
Module 2.7.3	Summary of Clinical Efficacy (PERSEPT 1)
Module 2.7.4	Summary of Clinical Safety (PERSEPT 1)
Module 5.2	Tabular Listing of all Clinical Studies
Module 5.3.5.1	PERSEPT 1 Clinical Study Report
Module 5.3.5.1	PERSEPT 1 Documentation of Statistical Methods
Module 5.3.5.1	PERSEPT 1 Statistical Analysis Plan

BLA 125641/0/1

Module 1.2	Response to Request
Module 5.3.5.1	Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM). Datasets for the completed study RB-FVIIa-006-13

BLA 125641/0/20

Module 1.11.3	Clinical Information Amendment
Module 5.3.5.1	Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM). Datasets for the completed study RB-FVIIa-006-13

BLA 125641/0/56

Module 1.11.4	Multiple Module Information Amendment
Module 5.3.5.1	Analysis Program

BLA 125641/0/59

Module 1.11.4	Multiple Module Information Amendment
Module 5.3.5.1	Study Data Tabulation Model (SDTM), and Analysis Data Model (ADaM). Datasets for the completed study RB-FVIIa-006-13

5.3 Table of Studies/Clinical Trials

Table 1 lists all the clinical studies in the LR769 clinical development program.

Table 1. Tabular Listings of all Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Completed									
PK,PD, and safety, Dose finding Phase 1b	GTC-FVIIa-005-11	5.3.4.2	Safety, PK, and PD	Dose escalation	LR769 at 25, 75, 225 µg/kg; Cohort 1: 1 dose of 25 µg/kg of LR769 Cohort 2: 1 dose of 75 µg/kg of LR769; Cohort 3: 1 dose of 225 µg/kg of LR769; Each dose was administered IV several weeks apart	Total=15 patients: 25 µg/kg LR769: 10 subjects 75 µg/kg LR769: 5 subjects from 25 µg/kg, and 5 newly enrolled subjects 225 µg/kg LR769: 5 subjects from 25 µg/kg, and 5 subjects from 75 µg/kg	Adult male subjects with Hemophilia A or B with or without inhibitors	Two administrations, at different dose levels at different time points; participation varied from a few weeks to a few months	Complete; full
Safety and Efficacy in Adolescents and Adults, Phase 3	RB-FVIIa-006-13 PERSEPT 1	5.3.5.1	To assess the efficacy and safety of 2 separate dose regimens (75µg/kg and 225 µg/kg) of LR769 for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or IX	Global, multi-center, Phase 3, Prospective, Open-label, Randomized, Cross Over Study. Two dose regimens (75µg/kg and 225 µg/kg) of LR769	75, 225 µg/kg LR769 IV; crossover every 3 months	27 randomized	Adolescent/ Adult Hemophilia A or B patients with inhibitors	No further treatment with study drug beyond the time point where a *Good* or *Excellent* response for this bleeding episode was noted	Complete; full
PK/PD analysis, Phase 1b	CHDR1201	5.3.3.5	Describe PK/PD behavior of LR769	FVIIa-activity and relation with PD markers data analysis	LR769 at 25, 75, 225 µg/kg	N=15 patients	Adult male subjects with Hemophilia A or B with or without inhibitors	Two single-dose administrations	Complete PK/PD Report

PK analysis, Phase 3	CHDR C084-001	5.3.3.5	Describe PK of LR769	FVIIa-activity and PK analysis of LR769, Process A vs Process B	LR769 75 and 225 µg/kg IV	N=14 patients (PK portion of study)	Adolescent/ Adult Hemophilia A or B patients with inhibitors	Until at least 352 treated bleeding episodes	Complete PK Report
Integrated Safety, Phase 1b and Phase 3	ISS (SAP, TLFs, datasets)	5.3.5.3	Pooled safety analysis from Phase 1B and Persept 1	N/A	LR769 at doses 25, 75, 225 ug/kg IV	N=42	Patients from Phase 1b and PERSEPT 1	N/A	Completed
Ongoing/Planned									
Safety and Efficacy in Pediatrics, Phase 3	LFB-FVIIa-007-14 PERSEPT 2	5.3.5.1	To assess the efficacy and safety of 2 separate dose regimens (75µg/kg and 225 µg/kg) of LR769 for the treatment of bleeding episodes in patients from birth to 12 years with Hemophilia A and B with inhibitors	Global, multicenter, Phase 3, prospective, open-label, randomized, crossover study. Two dose regimens (75µg/kg and 225 µg/kg) of LR769 .	75, 225 µg/kg LR769 IV; crossover every 3 months	N=11 enrolled as of 31 March 2016 (BLA data-cut-off) N=24 planned (12 patients from birth to <6 years old, and 12 patients ≥6 years to <12 years old)	Pediatric patients from birth to 12 years with Hemophilia A and B with inhibitors	Until at least 352 treated bleeding episodes	Ongoing
Safety and Efficacy in Surgical Setting, Phase 3	LFB-FVIIa-008-14 PERSEPT 3	5.3.5.2	To assess the efficacy of LR769 to prevent excessive bleeding and to achieve hemostasis in patients with Hemophilia A or B patients with inhibitors who are undergoing elective surgical or other invasive procedure	Global, multi-center, Phase 3, single-arm, open-label	(b) (4)				

Source: "BLA 125641, Module 5.2 Clinical Study Report: Tabular Listing of all Clinical Trials"

6. Discussion of Individual Studies/Clinical Trials

Insert text here

6.1 Trial #1 : PERSEPT 1

Insert text here

6.1.1 Objectives (Primary, Secondary, etc)

The primary objectives are:

- to assess the efficacy of two separate dose regimens of LR769 for the treatment of bleeding episodes in hemophilia A or B subjects with inhibitors to FVIII or FIX
- to assess the safety of LR769. This includes the immunogenic potential of the drug product.

6.1.2 Design Overview

PERSEPT 1 was a phase 3, multicenter, prospective, open-label, randomized, crossover study.

Phase A (Initial phase): Subjects did not have an active bleeding episode at that time and had not received treatment with any FVII(a) product within 24 hours prior to this administration. This administration is for the assessment of safety of LR769.

Phase B (Treatment phase): Subjects who completed Phase A began with an initial treatment regimen consisting of a 3-month period of treatment with the dose to which they were randomized. Subjects then crossed over to the alternate treatment regimen every 3 months until the end of the study. The study was to continue until at least 22 subjects were followed for at least 6 months after the first treatment with LR769 and until at least 352 bleeding episodes were treated.

6.1.3 Population

Male, 12 to 75 years of age, with a diagnosis of congenital hemophilia A or B of any severity, having at least 3 bleeding episodes of any severity in the past 6 months, and having one of the following:

a. a positive inhibitor test Bethesda unit (BU) ≥5 (as confirmed at screening by the institutional lab), or
b. a BU <5 but expected to have a high anamnestic response to FVIII or FIX, as demonstrated from the subject's medical history, precluding the use of FVIII or FIX products to treat bleedings, or
c. a BU <5 but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the subject's medical history.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects who meet all inclusion and exclusion criteria will be randomized to start with one of two treatment regimens:

- 75 μg/kg on-demand treatment by 2-minute bolus IV infusion within four hours of first symptoms of the bleeding. 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 eight administrations in total are allowed for mild to moderate bleedings.
- 225 μg/kg on-demand treatment by 2-minute bolus IV infusion within four hours of first symptoms of the bleeding. The initial 225 μg/kg treatment may be followed nine hours later with 75 μg/kg every three hours until the bleeding is successfully treated.

During Phase B, the starting dose was the same as the dose that subjects were randomized to in Phase A. Thereafter, the subjects was crossed over to the alternate treatment regimen every 3 months until the end of the study.

6.1.6 Sites and Centers

Subjects were screened at 13 study sites, and 11 sites randomized subjects: Bulgaria (1 site), Georgia (1), Poland (1), Russia (2), United Kingdom (1), Ukraine (2), and US (3subject).

6.1.8 Endpoints and Criteria for Study Success

Primary:
The primary efficacy endpoint was successful treatment of a mild/moderate bleeding episode at 12 hours after initial study drug administration, where successful treatment is defined as a combination of the following:

- Good or Excellent response to treatment of a bleeding episode. The physician rated the response as "none," "moderate," "good," or "excellent":
    - None: no noticeable effect of the treatment on the bleeding or worsening of patient's condition. Continuation of treatment with the study drug is needed.
    - Moderate (fair): some effect of the treatment on the bleeding is noticed, e.g., pain decrease or bleeding signs improvement, but bleeding continues and requires continued treatment with the study drug.
    - Good: symptoms of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) have largely been reduced by the treatment, but have not completely disappeared. Symptoms have improved enough to not require more infusions of the study drug.
    - Excellent: full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage). No additional infusion of study drug is required.
- No further treatment with study drug beyond time point for this bleeding episode
- No other hemostatic treatment needed for this bleeding episode
- No administration of blood products indicating continuation of bleeding beyond time point
- No increase of pain beyond time point that cannot otherwise be explained

The following null hypothesis will be tested by a one-sided test, with alpha = 0.0125 (adjusted from 0.025 to 0.0125 to account for multiplicity of testing each treatment regimen separately):

H_0: $p \leq 0.55$, where p is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours.

This analysis will be performed for each of the two treatment regimens. For the study to be considered successful, at least one of the two tests should reject the null hypothesis.

Secondary:

- Proportion of mild/moderate bleeding episodes with a "good" or "excellent" subject reported response at 12 hours.
- Time to assessment of a "good" or "excellent" response of mild/moderate bleeding episodes by the subject.
- Number of administrations and total amount of drug administered per mild/moderate bleeding episode.

Safety endpoints include immunogenicity testing and assessment of AEs (e.g., thromboembolic events).

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size:
With a true proportion of success of 0.70, a correlation among bleeding episodes for a given subject of 0.1, and an OPC of 0.55, a sample size of 22 subjects with a total of 352 mild/moderate bleeding episodes (assuming eight mild/moderate bleeding episodes per treatment regimen per subject) should provide statistical power ≥80%, with a Type 1 error rate of 0.0125 (adjusted from 0.025 to account for multiplicity of testing), using a one-sided, one-sample normal approximation test.

Analysis Populations:
The Enrolled Population is defined as all subjects who signed informed consent. Analyses of non-treatment emergent adverse events (non TEAEs) were done on this population.

The Safety Population is defined as all enrolled subjects who received at least one dose of study treatment. All Safety endpoints and baseline characteristics were analyzed on this population

The Treated Population is defined as all enrolled subjects 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 was analyzed as treated.

Statistical Methods:
Primary endpoint
For each LR769 dose, the proportion of successes was presented together with a 95% CI for the true proportion. The null hypothesis was tested using a one-sided, one-sample, normal approximation test and a test statistic Z obtained by dividing ($\hat{p}$ -0.55) by its estimated standard error. To account for the correlation between bleeding episodes from the same patient, the estimated standard error was calculated by the formula:

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

, where n is the number of patients, m_i is the number of episodes for the i^{th} patient,

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

The correlation is calculated by the formula

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

, where

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

The test was conducted at the one-sided 0.0125 significance level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing). In addition, the number of subjects, number of mild/moderate bleeding episodes, number of bleeding episodes successfully treated, number of failures, and number of missing values were summarized for each LR769 dose.

As sensitivity analyses, generalized estimating equations (GEE) logistic regression (SAS PROC GENMOD) and generalized linear mixed-effect model (SAS PROC GLIMMIX) analyses were used to assess whether any of the following variables had an impact on the primary efficacy endpoint for each dose:

- Treatment regimen
- Severity of hemophilia
- Type of bleeding episode (spontaneous vs. traumatic)
- Age of subjects
- Home treatment vs. treatment in hospital/hemophilia care center
- Time between start of bleeding and first study drug administration
- High titer vs. low titer inhibitor subjects (BU ≥5 vs. BU<5)

- Subjects with or without immune tolerance induction (ITI) therapy
- Anatomical location (joint, including whether a target joint was involved, mucocutaneous, muscle, soft tissue, and other)

The analysis was performed in two steps. First, separate univariate models were created to test the effect of the factors listed above on the primary efficacy endpoint. Then all of the variables with a p-value <0.1 from the univariate analyses were included in a multivariate model (treatment was part of the model regardless of the *p* value) as fixed effects. A compound symmetry covariance structure was used.

Proportions were compared between the two LR769 treatment doses using a normal approximation test statistics

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

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

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

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

, and

$$\hat{\rho}_1 = \frac{\sum_{i=1}^{n}\sum_{j=1}^{m_i}\sum_{j'=1}^{m_i}(x_{i,j}-\bar{x})(x_{i,j'}-\bar{x})}{\sum_{i=1}^{n}(m_i-1)\sum_{j=1}^{m_i}(x_{i,j}-\bar{x})^2}$$, 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 $\hat{\rho}_3$, is the Pearson sample correlation coefficient calculated using all ordered pairs of observations (x_{ij} , $y_{ij'}$) $i=1,2,\ldots,n$; $j= 1,2,\ldots,m_i$; $j'=1,2,\ldots,l_i$.

The proportion of successfully treated bleeding episodes and the p-value from the test was summarized for all subjects and by treatment regimen for the treated population.

Secondary endpoints

The proportion of mild/moderate bleedings with a "good" or "excellent" subject-reported response were analyzed similarly to the primary efficacy endpoint, except that no sensitivity analyses were performed. The number of administrations of study drug per bleeding episode and the total amount of study drug administered per bleeding episode was summarized on a bleeding episode level by actual treatment regimen used for a bleeding episode and overall using descriptive statistics. The comparison of the means in two treatment arms was performed using the repeated measures ANOVA.

Missing Data:

The primary efficacy analysis was performed based on a data-as-observed (DAO) approach, i.e., no imputation was made for missing values in the primary efficacy analysis. Sensitivity analyses were performed to examine the effect of missing data, if any, on the results of the primary efficacy endpoint. In one sensitivity analysis, all mild/moderate bleeding episodes for which the 12-hour assessment was missing were assigned as successes. In another sensitivity analysis, all such missing assessments of the bleeding episodes were assigned as failures.

6.1.10 Study Population and Disposition

Insert text here

6.1.10.1 Populations Enrolled/Analyzed

Twenty-seven subjects with hemophilia A or B were enrolled into study, and all 27 subjects are in the Safety and Treated populations.

6.1.10.1.1 Demographics

The enrolled population was predominantly white (92.6%) and non-hispanic (96.3%). All subjects in the study were male, as required by eligibility criteria. The age distribution was between 12 and 54 years, with a mean of 31 years. Five subjects were <18 years old, with 2 (15.4%) in the 75 μg/kg treatment regimen and 3 (21.4%) in the 225 μg/kg treatment regimen. Twenty-two subjects were ≥18 years old, with 11 subjects in each of the 75 μg/kg (84.6%) and 225 μg/kg (78.6%) regimens. Mean (SD) weight was lower in the 75 μg/kg regimen (61.4 kg) than in the 225 μg/kg regimen (71.2 kg); refer to Table 2.

Table 2. Subject Demographics and Baseline Characteristics (Safety Population)

Parameter		75 µg/kg (N=13)	225 µg/kg (N=14)	Overall (N=27)
Age (yrs)	n	13	14	27
	nmiss	0	0	0
	Mean (SD)	31.8 (12.10)	30.1 (12.98)	31.0 (12.35)
	Median	31.0	30.5	31.0
	Q1/Q3	24.0/39.0	19.0/38.0	19.0/39.0
	Minimum/Maximum	13/51	12/54	12/54
Age categorized [n(%)]	N of Patients	13	14	27
	< 18 years	2 (15.4%)	3 (21.4%)	5 (18.5%)
	>= 18 years	11 (84.6%)	11 (78.6%)	22 (81.5%)
Race [n(%)]	N of Patients	13	14	27
	Asian	1 (7.7%)	0 (0.0%)	1 (3.7%)
	Black Or African American	0 (0.0%)	1 (7.1%)	1 (3.7%)
	White	12 (92.3%)	13 (92.9%)	25 (92.6%)
Ethnicity [n(%)]	N of Patients	13	14	27
	Hispanic Or Latino	1 (7.7%)	0 (0.0%)	1 (3.7%)
	Not Hispanic Or Latino	12 (92.3%)	14 (100%)	26 (96.3%)
Sex [n(%)]	N of Patients	13	14	27
	Male	13 (100%)	14 (100%)	27 (100%)
Weight (kg)	n	13	14	27
	nmiss	0	0	0
	Mean (SD)	61.42 (16.359)	71.18 (23.177)	66.48 (20.416)
	Median	62.00	68.25	68.00
	Q1/Q3	56.40/72.00	58.00/88.00	56.40/78.00
	Minimum/Maximum	25.0/81.2	36.0/107.0	25.0/107.0

Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 10.1.3.1.1"

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

The majority of subjects have hemophilia Type A (25/27, 92.6%). There were only two hemophilia Type B subjects (both in the 225 µg/kg regimen). The majority of subjects (92.6%) had a hemophilia severity grade of "severe." Overall, 14 subjects (51.9%) had a BU ≥5. Eleven subjects (40.7%) had a BU <5 but were expected to have a high anamnestic response to FVIII or FIX, precluding the use of FVIII or FIX products to treat bleeding episodes. Two subjects (7.4%) had a BU <5 but were expected to be refractory to increased dosing of FVIII or FIX products to treat bleeding episodes.

Table 3. Summary of Disease History (Treated Population)

Parameter		Treatment Regimen at Randomization		Overall (N=27)
		75 µg/kg (N=13)	225 µg/kg (N=14)	
Type of Hemophilia [n (%)]	Type A	13 (100%)	12 (85.7%)	25 (92.6%)
	Type B	0	2 (14.3%)	2 (7.4%)
Hemophilia severity grade at Screening [n (%)]	Mild	0	0	0
	Moderate	1 (7.7%)	1 (7.1%)	2 (7.4%)
	Severe	12 (92.3%)	13 (92.9%)	25 (92.6%)
Factor [n (%)]	FVIII	13 (100%)	12 (85.7%)	25 (92.6%)
	FIX	0	2 (14.3%)	2 (7.4%)
Factor level (%)	Mean (SD)	0.38 (0.533)	0.35 (0.411)	0.36 (0.464)
	Median	0.10	0.20	0.10
	Q1/Q3	0.00/0.50	0.00/0.50	0.00/0.50
	Minimum/Maximum	0.0/1.8	0.0/1.0	0.0/1.8
Inhibitor status [n (%)]	BU <5	7 (53.8%)	6 (42.9%)	13 (48.1%)
	BU ≥5	6 (46.2%)	8 (57.1%)	14 (51.9%)
BU <5 but expected to have a high anamnestic response to FVIII or FIX [n (%)]	Yes	6 (46.2%)	5 (35.7%)	11 (40.7%)
	No	7 (53.8%)	9 (64.3%)	16 (59.3%)
BU <5 but expected to be refractory to increased dosing of FVIII or FIX [n (%)]	Yes	1 (7.7%)	1 (7.1%)	2 (7.4%)

Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 10.1.8.2"

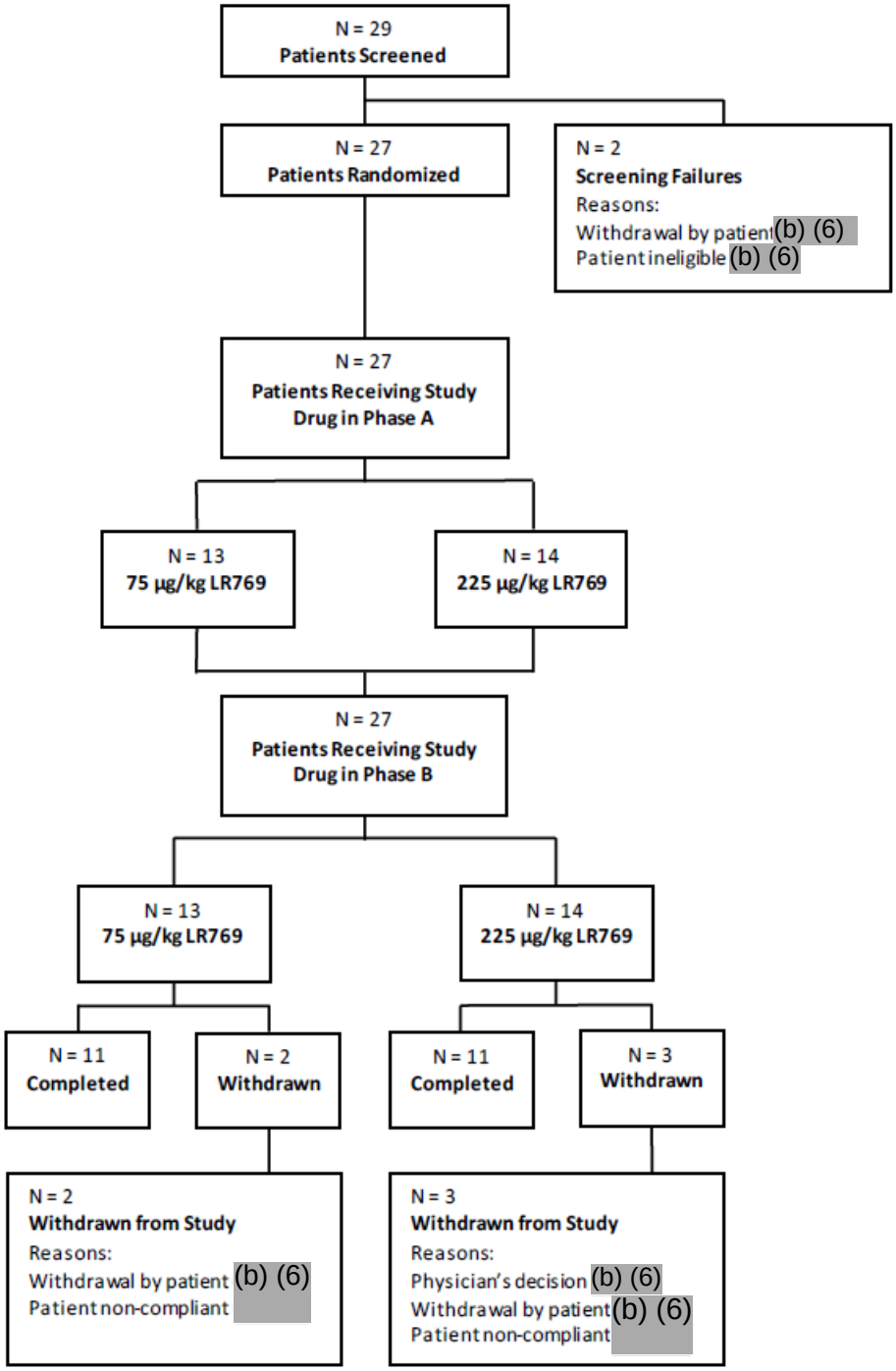
6.1.10.1.3 Subject Disposition

A total of 29 subjects signed informed consent for the study. Two subjects failed screening procedures. Thirteen subjects were randomized to the 75 µg/kg treatment regimen in Phase A and initial treatment in Phase B with the 75 µg/kg treatment regimen. Fourteen subjects were randomized to the 225 µg/kg treatment regimen in Phase A and initial treatment in Phase B with the 225 µg/kg treatment regimen. Five subjects discontinued the study early, all during Phase B. The reasons for discontinuation were as follows:

- Physician decision: one subject (b) (6) randomized to the 225 µg/kg treatment regimen was discontinued due to non-compliance and difficulty administering study drug independently
- Withdrawal by subject: one subject (b) (6) randomized to the 225 µg/kg treatment regimen discontinued due to personal issues at home, and one subject (b) (6) randomized to the 75 µg/kg treatment regimen for the reason that the low dose of study drug was not considered effective by the subject
- "Other:" one subject (b) (6) randomized to the 75 µg/kg treatment regimen and one subject (b) (6) randomized to the 225 µg/kg treatment regimen were discontinued at the applicant's request due to non-compliance.

No subject had a study interruption. Subject disposition is presented in Figure 1 and Table 4.

Figure 1. Subject Disposition



Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Figure 1"

Table 4. Disposition of Subjects (All Enrolled Subjects)

Patient Disposition	75 µg/kg N (%)	225 µg/kg N (%)	Overall N (%)
Enrolled	13 (100%)	14 (100%)	27 (100%)
Completed the Study	11 (84.6%)	11 (78.6%)	22 (81.5%)
Withdrew from the Study	2 (15.4%)	3 (21.4%)	5 (18.5%)
Primary Reason for Withdrawal:			
Physician Decision	0 (0.0%)	1 (7.1%)	1 (3.7%)
Withdrawal By Subject	1 (7.7%)	1 (7.1%)	2 (7.4%)
Other	1 (7.7%)	1 (7.1%)	2 (7.4%)
Number of Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)
Safety Population	13 (100%)	14 (100%)	27 (100%)
Treated Population	13 (100%)	14 (100%)	27 (100%)

Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 10.1.2"

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 5 presents the primary efficacy analysis results overall and by treatment regimen. Overall, there were 465 mild/moderate bleeding episodes. Treatment of 393 (393/465, 84.5%) of the mild/moderate bleeding episodes were determined to be treatment successes, 50 (10.8%) were deemed to be treatment failures, and 22 (4.7%) had missing values at 12 hours after initial study drug administration.

The observed percentages of successfully treated mild/moderate bleeding episodes (and 95% CIs) for each dose group, based on non-missing assessments, are as follows:

- 84.9% (202/238; 95% CI; 74.0%, 95.7%) for the 75 µg/kg regimen. Statistical testing of the null hypothesis comparing percentage of success to 55% was significant ($p < 0.001$) at the one-sided 0.0125 significance level.
- 93.2% (191/205; 95% CI; 88.1%, 98.3%) for the 225 µg/kg regimen. Statistical testing of the null hypothesis comparing percentage of success to 55% was significant ($p < 0.001$) at the one-sided 0.0125 significance level.

In addition, the observed percentage of successfully treated mild/moderate bleeding episodes for the 225 µg/kg regimen was greater than that for the 75 µg/kg regimen. The rate of treatment failures at 12 hours was approximately 2 times higher for the 75 µg/kg regimen than for the 225 µg/kg regimen (see Table 5).

Table 5. Primary Efficacy Endpoint: Proportion of Successfully Treated Mild/Moderate Bleeding Episodes at 12 Hours after Initial Study Drug Administration (Treated Population)

	Treatment Regimen at the Time of Mild/Moderate Bleeding Episode		Overall (N=27)[1]
	75 µg/kg (N=25)[1]	225 µg/kg (N=25)[1]	
Number of bleeding episodes	252	213	465
Number of successes	202 (80.2%)	191 (89.7%)	393 (84.5%)
Number of failures	36 (14.3%)	14 (6.6%)	50 (10.8%)
Number of missing	14 (5.6%)	8 (3.8%)	22 (4.7%)
Success proportion [95% CI][2]	0.849 [0.740, 0.957]	0.932 [0.881, 0.983]	0.887 [0.807, 0.967]
p-value[3]	<0.001	<0.001	<0.001
p-value[4]			0.020

[1] N in the column header indicates number of patients who had at least 1 bleeding episode treated with a given dose of study drug.

[2] Analysis was based on data as observed. No missing value imputation was made.

[3] p-value from 1-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient.

[4] p-value from 2-sided normal approximation test comparing proportions for the two treatment regimens, with adjustment for the correlation among bleeding episodes for a given patient.

Note: Stratified by actual treatment regimen at the time of the bleeding episode.

CI = confidence interval.

Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 14"

Reviewer Comment. On June 12, 2017, the clinical reviewer, P. Sharma, M.D., emailed me a list of ten observations she re-designated as failures instead of applicant's designation as successes. She requested the statistical analysis of the resulting dataset. I reclassified the outcomes for these ten successes as failures and reclassified all missing values as failures. I calculated the confidence intervals using PROC GLIMMIX. The lower confidence limit for the regimen 75 µg/kg was 0.5517 and lower confidence limit for the regimen 225 µg/kg was 0.6585. Both results exceeded the success criteria 0.55. From this worst case scenario it follows that the outcome of any imputation will not change the qualitative outcome of the study. Sensitivity analyses using the GEE and generalized linear mixed-effect models give similar results.

The clinical review team had several requests to the applicant regarding reclassification of bleeding episodes for various clinical reasons. On August 14, 2017, the FDA sent a final request to re-analyze the primary endpoint data with 15 bleeding episode outcomes reclassified. On August 23, 2017, the FDA received Amendment 59 in response to this final request. In the modified dataset, some outcomes were reclassified from success to failure and vice versa, and five missing values were reclassified as success or failure as well. The results of this additional analysis are presented in Table 5.1. Sensitivity analyses using the GEE and generalized linear mixed-effect models give similar results.

Table 5.1 Primary Efficacy Endpoint–Successful Treatment of Mild/Moderate Bleeding Episodes at 12 Hours (Treated Population; 15 outcomes reclassified:

	75 µg/kg (N=25)	225 µg/kg (N=25)	Overall (N=27)
Number of Mild/Moderate Bleeding Episodes	252	213	465
Number of Successes	197 (78.2%)	188 (88.3%)	385 (82.8%)
Number of Failures	44 (17.5%)	19 (8.9%)	63 (13.5%)
Number of Missings	11 (4.4%)	6 (2.8%)	17 (3.7%)
Success Proportion [95% CI]***	0.817 [0.723, 0.912]	0.908 [0.837, 0.980]	0.859 [0.784, 0.935]
p-value*	<0.001	<0.001	<0.001

Note: Numbers in the header indicate number of subjects who have at least one bleeding episode treated with a given dose of study drug.
** p-value from one-sided normal approximation test of H_0: p <= 0.55, where p is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given subject.*
**** Analysis is based on data as observed.*
Source: "BLA 125641/0/59, Module 5.3.5.1 Analysis Program, Table 10.2.1.1"

6.1.11.2 Analyses of Secondary Endpoints

Proportion of subject-reported mild/moderate bleeding episodes rated "good" or "excellent"

The proportion of mild/moderate bleeding episodes reported "good" or "excellent" by the subject is presented overall and by treatment regimen in Table 6. Results are nearly identical to those of the primary efficacy endpoint. Overall, 89.3% (396/443) of mild/moderate bleeding episodes had reported "good" or "excellent" responses at 12 hours after the initial study drug administration.

The observed percentages of successfully treated mild/moderate bleeding episodes (and 95% CIs) for each treatment regimen, based on non-missing assessments, are as follows:

- 85.7% (204/238; 95% CI; 75.0%, 96.4%) for the 75 µg/kg regimen. Statistical testing of the null hypothesis comparing percentage of success to55% was significant (p <0.001) at the one-sided 0.0125 significance level.
- 93.7% (192/205; 95% CI; 88.8%, 98.6%) for the 225 µg/kg regimen. Statistical testing of the null hypothesis comparing percentage of success to 55% was significant (p <0.001) at the one-sided 0.0125 significance level.

Table 6. Proportion of Mild/Moderate Bleeding Episodes with Subject-Reported "Good" or "Excellent" Responses at 12 Hours (Treated Population)

	Treatment Regimen at the Time of Mild/Moderate Bleeding Episode		
	75 µg/kg (N=25)[1]	225 µg/kg (N=25)[1]	Overall (N=27)[1]
Number of bleeding episodes	252	213	465
Number of successes	204 (81.0%)	192 (90.1%)	396 (85.2%)
Number of failures	34 (13.5%)	13 (6.1%)	47 (10.1%)
Number of missing	14 (5.6%)	8 (3.8%)	22 (4.7%)
Success proportion [95% CI][2]	0.857 [0.750, 0.964]	0.937 [0.888, 0.986]	0.894 [0.816, 0.972]

[1] N in the column header indicates number of subjects who had at least one bleeding episode treated with a given dose of study drug.
[2] Analysis was based on data as observed. No missing value imputation was made.
Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 20"

Results of the analysis for the secondary efficacy endpoint are nearly identical to those of the primary efficacy endpoint, as only three bleeding episodes required the need for more objective criteria stipulated for determination of treatment success.

Time to assessment of "good" or "excellent"

Time to subject assessment of "good" or "excellent" response for mild/moderate bleeding episodes is presented overall and by treatment regimen in Table 7. Of the mild/moderate bleeding episodes, 95.2% in the 75 µg/kg regimen and 97.7% in the 225 µg/kg regimen of the subject-reported responses were assessed as "good" or "excellent". The median time to assessment of "good" or "excellent" response was approximately 3 hours shorter in the 225 µg/kg regimen (3.00 hours) compared with the 75 µg/kg regimen (5.98 hours).

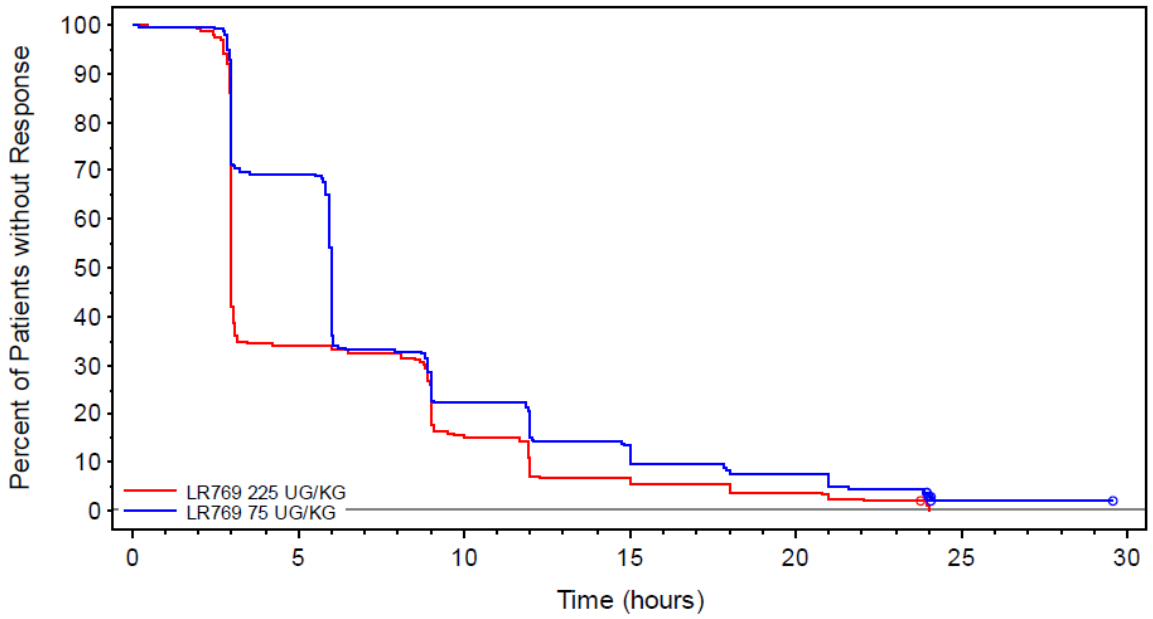
Table 7. Time to Subject Assessment of "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes (Treated Population)

	Treatment Regimen at the Time of Mild/Moderate Bleeding Episode		
	75 µg/kg (N=25)[1]	225 µg/kg (N=25)[1]	Overall (N=27)[1]
Bleeding episodes with event	240 (95.2%)	208 (97.7%)	448 (96.3%)
Censored bleeding episodes	7 (2.8%)	1 (0.5%)	8 (1.7%)
Missing	5 (2.0%)	4 (1.9%)	9 (1.9%)
Kaplan-Meier estimate (hours)			
Q1 (CI)	3.00 [3.00, 3.25]	2.97 [2.95, 3.00]	3.00 [NA, NA]
Median (CI)	5.98 [5.95, 6.00]	3.00 [NA, NA]	5.92 [3.08, 5.95]
Q3 (CI)	9.00 [8.92, 12.00]	9.00 [8.53, 9.00]	9.00 [8.92, 9.00]
Cox regression hazard ratio			0.71

[1] N in the column header indicates number of subjects who had at least one bleeding episode treated with a given dose of study drug.
Note: Stratified by actual treatment regimen at the time of the bleeding episode.
CI = confidence interval; Q = quartile.
Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 22"

The Kaplan-Meier plot of subject assessment of "good" or "excellent" response for mild/moderate bleeding episodes is shown in Figure 2.

Figure 2. Subject Assessment of "Good" or "Excellent" Response for Mild/Moderate Bleeding Episodes, Kaplan-Meier Estimate (Treated Population)



Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Figure 2"

Number of administrations and total amount of administered drug

The number of administrations and total amount of study drug administered per mild/moderate bleeding episode are presented overall and by treatment regimen (regimen the subject was receiving at the time the bleeding episode occurred) in Table 8. The mean (SD) number of administrations of study drug per mild/moderate bleeding episode was 2.5 (1.75) for the 75 µg/kg regimen and 1.4 (0.96) for the 225 µg/kg regimen. For the 75 µg/kg treatment regimen, the mean (SD) total amount of study drug (µg/kg) administered per mild/moderate bleeding episode was 187.87 (131.80) µg/kg, which corresponds with approximately 2.5 mean administrations of 75 µg/kg of drug. For the 225 µg/kg treatment regimen, the mean (SD) total amount of study drug (µg/kg) administered per mild/moderate bleeding episode was 252.96 (78.97) µg/kg, which corresponds with 1.4 mean administrations of the treatment regimen for this dose group, i.e., subjects received an initial injection of 225 µg/kg followed by 75 µg/kg, if needed.

Table 8. Number of Administrations of Study Drug and Total Amount of Study Drug Administered Per Mild/Moderate Bleeding Episode (Treated Population)

Parameter (Per Mild / Moderate Bleeding Episode)	Statistic	Treatment Regimen at the Time of the Mild/Moderate Bleeding Episode		Overall (N=27)[1]
		75 µg/kg (N=25)[1]	225 µg/kg (N=25)[1]	
Number of Administrations of Study Drug	n	252	211	463
	nmiss[2]	0	2	2
	Mean (SD)	2.5 (1.75)	1.4 (0.96)	2.0 (1.56)
	Median	2.0	1.0	1.0
	Q1/Q3	1.0/3.0	1.0/1.0	1.0/2.0
	Min/Max	1/12	1/6	1/12
Total Amount of Study Drug Administered (µg/kg)	n	251	211	462
	nmiss[2,3]	1	2	3
	Mean (SD)	187.868 (131.7982)	252.963 (78.9732)	217.598 (115.3901)
	Median	149.680	225.090	225.000
	Q1/Q3	75.230/225.000	225.000/233.470	149.200/227.430
	Min/Max	73.62/909.72	75.00/676.26	73.62/909.72

[1] Numbers in the header indicate number of subjects who have at least one bleeding episode treated with a given dose of study drug.
[2] On two occasions, Subject (b) (6) received one 225 µg/kg dose of study drug for two simultaneous bleeding episodes (i.e., he had two bleeding episodes in two different anatomical locations at the same time). For each occasion, the exposure data was set to 'missing' for one of the simultaneous bleeding episodes to prevent double counting, since only one treatment was given on each occasion.
[3] Subject (b) (6) (75 µg/kg regimen) administered study drug for a bleeding episode on (b) (6), but did not record dose and actual volume administered, or stop time of study drug administration in the subject diary; he did indicate that he administered one 5-mg vial of study drug and the lot number. Therefore, this subject's data is missing for total amount of study drug administered.
Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 23"

6.1.11.3 Subpopulation Analyses

Sex and Race

Subgroup analyses by sex and race were not performed because all subjects were male, and only two (7.4%) were non-white.

Age

For subjects who were <18 years of age (n = 5), the proportion of mild/moderate bleeding episodes that were successfully treated was numerically higher for both treatment regimens (Table 9), compared with results of the main primary efficacy analysis.

- 95.3% (41/43; 95% CI; 84.0%, 100.0%) for the 75 µg/kg regimen.
- 94.3% (33/35; 95% CI; 88.0%, 100.0%) for the 225 µg/kg regimen.

For subjects who were ≥18 years of age (n = 22), the proportion of mild/moderate bleeding episodes that were successfully treated was numerically lower for 75 µg/kg treatment regimen and higher for 225 µg/kg treatment regimen (Table 9), compared with results of the main primary efficacy analysis.

- 82.6% (161/195; 95% CI; 69.4%, 95.7%) for the 75 µg/kg regimen.
- 93.1% (161/173; 95% CI; 87.0%, 99.1%) for the 225 µg/kg regimen.

Table 9. Successful Treatment of Bleeding Episodes (Regardless of Severity) at 12 Hours (Treated Population) by Age at Bleeding Episode

Age		75 µg/kg (N=25)	225 µg/kg (N=25)	Overall (N=27)
<18	Number of Bleeding Episodes	44	35	79
	Number of Successes	41 (93.2%)	33 (94.3%)	74 (93.7%)
	Number of Failures	2 (4.5%)	2 (5.7%)	4 (5.1%)
	Number of Missings	1 (2.3%)	0 (0.0%)	1 (1.3%)
	Success Proportion [95% CI]****	0.953 [0.840, 1.000]	0.943 [0.880, 1.000]	0.949 [0.869, 1.000]
>=18	Number of Bleeding Episodes	208	181	389
	Number of Successes	161 (77.4%)	161 (89.0%)	322 (82.8%)
	Number of Failures	34 (16.3%)	12 (6.6%)	46 (11.8%)
	Number of Missings	13 (6.3%)	8 (4.4%)	21 (5.4%)
	Success Proportion [95% CI]****	0.826 [0.694, 0.957]	0.931 [0.870, 0.991]	0.875 [0.779, 0.971]

Note: Table is stratified by actual treatment arm at bleeding episode.
Note: Numbers in the header indicate number of subjects who have at least one bleeding episode treated with a given dose of study drug.
**** Analysis is based on data as observed. No missing value imputation is made.
Source: "BLA 125641, Module 5.3.5.1 Clinical Study Report: RB-FVIIa-006-13, Table 10.2.2.3.a"

Low-titer Inhibitors

For subjects with low-titer inhibitors (BU <5, n = 13), the proportion of successes was 69.6% (80/115) for the 75 µg/kg regimen and 84.0% (84/100) for the 225 µg/kg regimen (compared with 85.7% and 93.4%, respectively, for the primary efficacy analysis shown in Table 5).

6.1.11.4 Dropouts and/or Discontinuations

A sensitivity analysis was performed in which all bleeding episodes with missing primary efficacy endpoint values were assigned as failures. The results are presented in Table 10 (compare with Table 5). The lower confidence limits are slightly less than in Table 5 (0.698 vs. 0.740 for the 75 µg/kg regimen and 0.821 vs. 0.932 for the 225 µg/kg regimen, however, it is substantially above the hypothesis tested OPC of 55%. Therefore, the relatively small number of dropouts (14 of 252, 5.6%) for the 75 µg/kg regimen and 8 of 213, 3.8% for 225 regimen), did not impact meeting the success criteria.

Table 10. Primary Efficacy Endpoint Sensitivity Analysis–Missing Responses Treated as Failures.

Missing assessments treated as failures			
Number of bleeding episodes	252	213	465
Number of successes	202 (80.2%)	191 (89.7%)	393 (84.5%)
Number of failures	50 (19.8%)	22 (10.3%)	72 (15.5%)
Success proportion [95% CI]	0.802 [0.698, 0.905]	0.897 [0.821, 0.973]	0.845 [0.759, 0.932]
p-value[2]	<0.001	<0.001	<0.001

[1] N in the column header indicates number of subjects who had at least 1 bleeding episode treated with a given dose of study drug.

[2] p-value from 1-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given subject.
Source: "BLA 125641, Module 5.3.5. 2 Clinical Study Report: Table 16"

6.1.12 Safety Analyses

Insert text here

6.1.12.3 Deaths

No deaths occurred during the study.

6.1.12.4 Nonfatal Serious Adverse Events (SAE)

Subject (b) (6) (19-year-old white male with severe hemophilia A) experienced two AEs (acute tonsillitis and subarachnoid hemorrhage) that were classified as one SAE by the investigator because they resulted in one hospitalization.

6.1.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events are considered AEs of special interest for anti-hemophilic factor products. No thromboembolic events were reported in this study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

One pivotal study (PERSEPT 1) was conducted and enrolled 27 male subjects, 5 subjects <18 years of age and 22 subjects ≥18 years of age; 22 subjects completed the study.

Overall, there were 465 mild/moderate bleeding episodes. Treatment of 393 (84.5%) of these bleeding episodes were determined to be treatment successes, 50 (10.8%) were deemed to be treatment failures, and 22 (4.7%) had missing values at 12 hours after initial study drug administration. With the one-sided 0.0125 significance level of success for each dose regimen (75 μg/kg and 225 μg/kg), the family-wise type I error rate was controlled at the one-sided 0.025 level. Given that the p-value is <0.001 for each dose regimen, the trial rejected the null hypotheses that the true proportion of successfully treated mild/moderate bleeding episodes at 12 hours is less or equal to 0.55.Therefore, the study met its primary efficacy outcome success criterion for both doses.

There were no deaths during the clinical study. No thromboembolic events, or immune or allergenic responses in adolescent or adult subjects were observed.

10.2 Conclusions and Recommendations

There were no statistical issues in this submission. The confidence intervals and p-values were calculated correctly. Results of PERSEPT 1 appear to support the use of LR769 in adolescent and adult subjects with hemophilia A or B with inhibitors for on-demand treatment and control of bleeding episodes. Of note, only two subjects with hemophilia B were included in the study, limiting direct generalizability of the data to this population. I

defer to the clinical review team regarding the generalizability of data in subjects with hemophilia A with inhibitors to the population with hemophilia B with inhibitors.