BLA Clinical Review Memorandum

Application Type	Original Application
STN	125641/0
CBER Received Date	10/13/2016
PDUFA Goal Date	10/13/2017
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Poornima Sharma
Review Completion Date / Stamped Date	10/13/17
Supervisory Concurrence	Bindu George, M.D. Tejashri Purohit-Sheth, M.D.
Applicant	LFB USA,Inc.
Established Name	Coagulation Factor VIIa (Recombinant)
(Proposed) Trade Name	Sevenfact
Pharmacologic Class	Recombinant
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single use vials containing 1 (b) (4) 5 mg for reconstitution with sterile water
Dosing Regimen	75mcg/kg repeated every 3 hours until hemostasis is achieved or 225mcg/kg; If hemostasis is not achieved within 9 hours, additional 75mcg/kg doses may be administered every 3 hours as needed to achieve hemostasis.
Indication(s) and Intended Population(s)	On-demand treatment and control of bleeding in adolescent and adult patients with hemophilia A or B with inhibitors to Factor VIII and IX
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

Glossary

AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
DIS	Division of Inspections and Surveillance
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NDA	new drug application
NME	new molecular entity
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PSA	prostate-specific antigen
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
RTF	refuse to file
SAE	serious adverse event

1.Executive Summary

SevenFact (LR 769) is a recombinant human factor VII coagulation factor. The original BLA seeks the indication for on-demand treatment of bleeding episodes in adults and adolescent hemophilia A and B patients with inhibitors to Factors VIII or IX for both at home administration and in the hospital setting for the treatment of bleeding episodes.

The development of inhibitors to Factor VIII or Factor IX is the most significant complication of hemophilia treatment and occurs in up to 33% of patients with severe hemophilia A and 3% of patients with severe Hemophilia B. Patients with low responding inhibitors (<5 BU [Bethesda Units]) continue treatment with factor replacement at the same or a higher dose. However, once the inhibitor titer is >5 BU, then factor replacement is ineffective and bypassing agents are needed. Currently, activated prothrombin complex concentrate and recombinant factor VIIa are approved as bypassing agents to treat bleeding episodes in subjects with hemophilia A and B with inhibitors.

The clinical trial providing primary evidence of efficacy was Study RB-FVIIa-006-13, which was a Phase 3 trial that assessed the safety, PK, and efficacy of two doses (75 µg/kg and 225 µg/kg) of SevenFact in hemophilia A and B subjects with inhibitors for the treatment of bleeding episodes in adults and adolescent subjects. The two doses evaluated in the Phase 3 study were selected based on the pharmacokinetic assessments from a single arm Phase 1 study evaluating three doses.

The primary efficacy endpoint was the proportion of mild/moderate bleeding episodes that were successfully treated as compared to an objective performance criterion (OPC) of 0.55. The OPC was derived from historical data from treatment with other bypassing agents. The protocol specified success was defined as statistically significant higher success compared to OPC. This study was powered to detect a 15% difference (from the OPC of 55% to the expected success rate of 70% for SEVENFACT) at 80% power with an alpha of 0.0125 (1-sided) for each of the treatment regimens. Thus, the study was designed to evaluate the efficacy of each of the treatment regimens. Primary efficacy assessment at 12 hours was based on a rating that included a 4-point hemostatic scale, need for transfusions or additional treatment of bleeding events and pain control beyond the 12-hour time point.

The FDA clinical reviewer identified clinical issues that were related to the efficacy assessment methods. The 4- point hemostatic scale is a subjective scale particularly in this open label study, since the 4-point scale relied primarily on control of pain as a reflection of joint bleeding events. The limitations of the primary efficacy assessment methods were communicated to the Applicant during the conduct of the clinical study. The Applicant was asked to include

additional assessment parameters to the 4- point scale, for example, range of motion and swelling. Although these parameters were included in the assessment scale, these parameters were not included in the patient's data capture plan in their diary. The Applicant modified the efficacy assessment to include a stand alone pain criterion. In addition to the pain assessment that was already a component in the 4-point hemostatic efficacy scale. During the review of the primary efficacy assessment, discordance in pain assessment between the 4-point scale and the additional pain score criteria was observed. Pain assessments were confounded by concomitant analgesic use which in turn affected the assessment of hemostatic efficacy. Thus, during the review, there were differences between the efficacy outcomes as noted by the Applicant and the FDA clinical reviewer. The primary efficacy outcome was revised after pain assessments and hemostatic efficacy outcomes were re-adjudicated for events confounded by analgesic use. In some instances of readjudication, subjects considered to have missing data for efficacy outcomes were considered by the clinical reviewer to have successful outcomes. The Applicant and the FDA clinical team reached an agreement on the final adjudication of the efficacy outcomes and the primary efficacy analyses were then performed based on the agreement. The results of the primarily efficacy analyses (see below) per the readjudicated outcomes are considered adequate to support an efficacy claim.

The efficacy results presented here represent the FDA reviewer's analysis of the results based on the readjudicaiton of efficacy outcomes. The proportion of successfully treated bleeding events for the 75 mcg/kg arm was 81.7 %(95% CI 72.3%-91.2%) and 90.8% for 225mcg/kg arm (95% CI 83.7%-98%). The study met its primary efficacy endpoint with a one sided p value of 0<.001. The 225 mcg/kg dose was associated with a higher success rate, lower failure rate, and a fewer mean number of administrations compared to 75 mcg/kg dose.

SevenFact was tolerated well with no occurrence of neutralizing antibodies to Factor VIIa or thromboembolic events. The main adverse events included fever and infusion site discomfort and hematoma. There were no substantial differences in the adverse events between the two doses.

The review team recommends approval of both doses for treatment of mild and moderate bleeding events as both doses met the primary efficacy endpoint. Only 3 severe bleeding events were included in this trial limiting the applicability of the results to only mild and moderate bleeding events.

Manufacturing of drug product was switched to a larger scale process (Process B) during the conduct of the Phase 3 trial and approximately 30% of bleeding events were treated with the Process B drug product. Comparison of PK parameters between Process B and Process A (smaller scale production) revealed increased Cmax and AUC for Process B drug product at 225 mcg/kg dosing. Although the root cause of the differences in the PK parameters between Process B and Process A have not been identified, issues regarding the reliability

of the potency assay are being considered as a potential issue. From a clinical review perspective, no safety issues related to thrombosis were noted despite the increased Cmax and AUC related to Process B. Within the 225 mcg/kg dosing arm, sixty eight percent (68.5%) of the bleeding events were treated with Process A product ,sixteen percent (16%) of the bleeding events were treated with Process B product and sixteen percent (15.5%) were treated with product manufactured with Process B product . Thus, the dose administered should be interpreted in the context of the implications related to 1) the potential for potency assay issues between the products manufactured via Process A and Process B and 2) that the evaluation of safety is limited as only 34 (16%) of bleeding events randomized to 225 mcg/kg arm were treated with the Process B product. Despite the differences in the pharmacokinetic parameters between the products manufactured from Processes A and B, the primary efficacy outcomes for subjects dosed at 225 mcg/kg and received Process A product vs. Process B product were concordant. Therefore, the efficacy results of the study are valid and no safety concerns were identified.

During the review of this BLA, several deficiencies were identified by the CMC team in the manufacturing process for recombinant coagulation Factor VIIa. There were repeated instances of visible particulates found in the reconstituted final drug product during release testing and stability testing. During the late cycle meeting, the Applicant stated that the neutralizing anti-drug antibody assay was validated for (b) (4) samples but the testing was done on (b) (4) samples raising concerns about the validity of the immunogenicity data from the 2 clinical trials.These findings did not impact the clinical review and assessment of both safety and effiacacy outcomes. Although, neutralizing antibodies to FVII were not identified, the interpretation of these findings should be made within the context of the pending CMC assessments related to immunogenicity.

A clinical study is ongoing evaluating efficacy and safety of Sevenfact in subjects <12 years of age. The Applicant has requested deferral for this age group. This application was presented to the Pediatric Review Committee (PeRC), the deferral request was discussed and the PeRC recommended that a pediatric deferral for patients < 12 years could be granted if a marketing approval is planned.

Recommendation: Study RB-FVIIa-006-13 is an adequate and well controlled study that demonstrated efficacy of Sevenfact at 75 µg/kg and 225 µg/kg over historical control for the treatment (on-demand) of bleeding episodes in adults and adolescents. This conclusion is based on the observed improvement in hemostatic efficacy as compared to historical control. There were no substantial safety concerns or risks identified that warrant a post marketing study or additional pre-marketing studies. However, if discrepancies in the potency assays between Process A and B are noted, the sponsor may need to re-analyze the dose administered for all subjects to ensure that the recommended dose of

75 and 225 µg/kg are the "true doses" based on the results of the final potency assay. Recommendations for any additional safety assessments for the dose based on Process B product alone may depend on the magnitude of difference between the dose determined by the current potency assay and the future potency assay.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary
All patients in both the studies were male as required by eligibility criteria. The mean age of participants from both studies was 31.6 years (range 12-61 years). The baseline demographics from both studies is summarized below-

Table 1: Study 1 and 2 Demographic Summary (n=42)

Age (years)	<18 years	5 (11.9%)
	≥ 18 years	37 (88%)
Race	White	35 (83%)
	Asian	3 (7%)
	Black/African	2 (4.7%)
Ethnicity	Hispanic/Latino	2 (4.7%)

Source :CSR ; Persept 1 and GTC-FVIIa-005-11

GTC-FVIIa-005-11 was a Phase1 trial that evaluated the pharmacokinetics and safety of SEVENFACT. The phase 3 trial RB-FVIIa-006-13 was a trial that evaluated the efficacy and safety of this product.
The analysis of both the studies can only be combined to interpret safety results as GTC-FVIIa-005-11 was conducted in subjects in the non-bleeding state. Overall demographics indicate a limited sample size of Hispanics, Blacks and Asians making it challenging to reach conclusions about pharmacokinetics, efficacy and safety in these subgroups. However, the efficacy of SEVENFACT is based on activating Factor X and generating thrombin. This mechanism of action is not expected to be influenced by differences in ethnicity. Safety concerns about the class of recombinant Factor VIIa include immunogenicity and thromboembolism and are considered to be independent of ethnicity. It is reasonable to extrapolate efficacy and safety data from the white population to the other ethnic groups with this product. In the Phase 3 trial, 11.9% of enrolled subjects were less than 18 years of age. No differences in efficacy and safety were noted between the adult and adolescent population in this trial

2.Clinical and Regulatory Background

SEVENFACT is a recombinant human coagulation Factor VIIa. This product is produced from the expression of human Factor VII gene under the control of (b) (4) specific promoter in mammary glands of transgenic rabbits. SEVENFACT is isolated and purified from the milk of transgenic rabbits and is activated during the purification process.

Indication that is sought in current BLA includes on-demand treatment of bleeding episodes in adults and adolescent hemophilia A and B patients with inhibitors to factor VIII and IX, recommended for both at home and in hospital setting under the supervision of a health care provider experienced in treatment of bleeding disorder.

2.1 Disease or Health-Related Condition(s) Studied

Hemophilias are X- linked inherited deficiencies of coagulation Factor VIII and IX that result in lifelong bleeding disorders. Hemophilia has an estimated global prevalence of approximately 400,000.

The development of inhibitors to Factor VIII or Factor IX is the most significant complication of hemophilia treatment and occurs in up to 33% of patients with severe hemophilia A and in 3% of patients with severe Hemophilia B. Patients with low responding inhibitors (<5 BU) continue treatment with factor replacement at the same or higher dose. For patients with high responding titers (≥ 5 BU/ml), factor VIII (hemophilia A) or IX (hemophilia B) replacement is ineffective and bypassing agents are needed. Bypassing agents such as Factor VIIa generate thrombin by bypassing Factor VIII and IX.

Several patient and treatment related factors can predict the development of inhibitors. Specific mutations associated with inhibitors include nonsense mutations, Intron 22 inversion and large deletions. The type of Factor VIII mutation may also influence the inhibitor titer as evidenced by 68.8% of patients with large deletions having high titer inhibitors compared to 21% with missense mutations and 30-40% with all other mutation types.

Several small cohort studies indicate that the age at first infusion of < 6 months is a risk factor for inhibitor development. It is felt now that age is a surrogate marker for severity of disease requiring early intervention. Among previously untreated patients (PUPs), risk factors for inhibitor development include surgery requiring Factor VIII replacement and ≥ 5 consecutive days of factor VIII treatment at first exposure as may be the case with peri-operative or on-demand treatment. Patients who receive regular prophylaxis (at least once weekly) as initial exposure have reduced risk of inhibitor formation. Patients of African or Hispanic heritage or with a family history of inhibitors are at higher risk for inhibitor development. (Witmer et al, 2013, Kempton et al, 2008).

Recently published SIPPET trial suggests that treatment with recombinant Factor VIII products compared to plasma derived products is associated with increased risk of factor inhibitors in previously untreated subjects with hemophilia A (Peyvandi et al, 2016). Based on review of additional clinical data from trials and observational studies, increased immunogenicity of recombinant Factor VIII products remains controversial.
Patients with hemophilia and inhibitors experience severe morbidity with recurrent episodes of joint, muscle and deep tissue bleeding events which can be limb and life threatening. Recurrent joint bleeding events lead to synovial inflammation, hypertrophy leading to more bleeding episodes and progressive damage to cartilage and subchondral bone. This leads to progressive severe arthropathy which can significantly reduce health status and quality of life in patients.

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

Patients with hemophilia and high responding Factor VIII / IX inhibitors require bypassing agents for bleeding episodes or in the perioperative setting. Currently available therapies include Activated Prothrombing ComplexPCC Concentrate (PCC) (i.e.FEIBA) and recombinant Factor VIIa (NOVOSEVEN). Dosing of FEIBA is 50-100 U/kg every 6- 12 hours. The FDA approved dose of Novoseven is 90 mcg/kg every 2-3 hours until hemostasis is achieved.

Therapy with one bypassing product can be effective even if another bypassing product has failed. In a study comparing FEIBA to NOVOSEVEN in hemophilia subjects with inhibitors, the overall hemostatic efficacy of both products was equivalent as assessed by the rate of hemostasis. Approximately, 30% of patients in each arm of the study derived greater hemostatic efficacy from one product compared to the other. Hence, bypass therapy needs to be individualized. From a safety perspective, the rate of thrombosis with both products appears to be equivalent. (Astermark et al, 2007) Activated PCC is associated with pro-thrombotic risk of venous, arterial thrombosis and disseminiated intravascular coagulation (DIC) and severe hypersensitivity including anaphylactoid reactions. Patients with hemophilia B with inhibitors can have anaphylactic reactions to Factor IX which is present in activated PCCs. Since FEIBA is a plasma-derived product, it carries the risk of transmission of infectious agents including Creutzfeldt-jakob disease agent.

NOVOSEVEN has no potential to induce an anamnestic response to FVIII or FIX inhibitors. The main safety concerns with NovoSeven include arterial/ venous thrombosis and allergic reactions.
Neutralizing inhibitors have not been not reported with either agent in hemophilia patients with inhibitors.

Table 2: Available Therapies for treatment of bleeding in severe hemophilia patients with inhibitors to FVIII or FIX

Product	Category	Half Life	Indications	Year Approved
FEIBA	Plasma derived	4-7 hours	Control and prevention of bleeding episodes Perioperative Management Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.	2013
Novoseven	Recombinant	2.6-3.1 hours	-Treatment of bleeding episodes in adults and children with hemophilia A or B with inhibitors	1999
			Peri-operative management in adults and children with hemophilia A or B with inhibitors,	2006

2.3 Safety and Efficacy of Pharmacologically Related Products

See Section 2.2

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Human subjects were exposed for the first time to this product under IND 15183.This product is not approved in any foreign countries.

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

A pre-IND meeting was held on December 13, 2011 during which the FDA provided advice regarding the

- Proposed dose in the Phase1 trial
- The design of the Phase 3 trial with regard to the definition of a) study success criteria, b) the use of historical data (please see below the discussions that occurred following the IND submission for details) c) blinded adjudication of hemostatic efficacy and d) safety monitoring for thromboembolic risks and for immunogenicity.
- Conducting a second Phase 1 dose finding study to explore the safety of the 90 mcg/kg dose given the manufacturing changes.

IND interactions particularly with regard to the design of the Phase 3 study were related to a) including more objective criteria (for example, number of doses required to control bleeding) to assess hemostatic efficacy b) safety monitoring and study stopping for development of neutralizing antibodies to FVII, monitoring plans for thromboembolic events and c) revisions to the statistical analysis plan to include a plan for handling missing data and justify sample size.

In a separate communication following review of the revised protocol (Version 5) in August 2015, the FDA clinical reviewer requested a) additional objective assessment criteria to distinguish between "moderate" and "good" hemostatic response b) revision of the eligibility criteria and primary efficacy analysis plan to include severe bleeding events. In this communication, the sponsor was informed that although the statistical plan included testing of both the 75 mcg/kg and 225 mg/kg doses against the OPC for efficacy, the inclusion of one or both doses for a marketing approval would be a review issue.

During the pre-BLA interaction, the discussion focused on the pediatric plans, CMC issues and a request to communicate and submit a new animal drug application with the Center for Veterinary Medicine (CVM) due to the use of the transgenic rabbits.

2.6 Other Relevant Background Information

None.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was sufficiently organized to allow complete clinical review without difficulty. The submission consisted of five modules in the common technical document structure.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Three sites were inspected, two domestic and one foreign as per Table 3 below.

Table 3: Clinical Site Inspections

Study Site	Site Name	Location	Form FDA 483 issued	Final inspection classification
26	Kyiv City Clinical Hospital #9	Ukraine	No	NAI
19	Rush University	Chicago,IL	No	NAI

20	University of Colorado Hemophilia and Thrombosis Center	Aurora,CO	No	NAI

NAI-No action Indicated.
There were no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

3.3 Financial Disclosures

Complete financial disclosures were provided for all studies and investigators. None of the investigators were noted to have disclosable financial interests. Thus, review of the financial disclosures did not identify issues that could unfavorably impact the clinical review of this submission.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Major deficiencies related to CMC issues were a) presence of particulate materials noted in the testing and stability studies b) deficiencies with the bulk manufacturing process c) product related stability issues that impact the shelf-life d) analytical methods for assessment of extractables and leachables. As these issues are being addressed through multiple interactions with the Applicant, please refer to the CMC memo for the final review status of these deficiencies. Potency assays related to Process A and B are described below and in Section 4.4.

4.2 Assay Validation

Potency assay issues are being explored as the root cause of the PK differences noted between the product manufactured under Process A and B. Assay re-validation reports have been submitted and are under review. Please refer to the clinical pharmacology and CMC review memo for updated information and plans, if any for additional testing.

During the late cycle meeting, the Applicant informed the FDA that (b) (4) samples were used to validate the neutralizing anti-drug antibody assay. However, b) (4) samples were used to perform the immunogenicity studies in the clinical studies. Therefore, the interpretability and validity of the immunogenicity study results may be impacted depending on the outcomes that demonstrate comparability of the validation plans between the (b) (4) and (b) (4) samples.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to Pharmacology/Toxicology review memo for complete details. Toxicology studies were conducted in cynomolgus monkeys to support the safe use of SEVENFACT in humans. The administration of SEVENFACT by once daily intravenous injection to the monkeys at 0, 0.1, 0.3, 1 and 3 mg/kg/day resulted in shortening of the prothrombin times at all dose levels, decreases in fibrinogen at ≥ 1.0 mg/kg/day and decrease in platelet count in one animal at 3.0 mg/kg/day. Thrombosis of the right ventricle of the heart was noted in two animals at 3.0 mg/kg/day and was considered to be directly related to the pharmacological action of LFB-rFVIIa.

Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 1.0 mg/kg. Another study evaluating the effect of SEVENFACT given daily on fertility of male Sprague-Dawley rats revealed an increased incidence and severity of infusion site changes at ≥ 1mg/kg/day. There was no effect on male reproductive performance at any dose level.

The pharmacology toxicology studies did not reveal unanticipated risks to humans that would warrant inclusion of the safety information in the label.
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4.4 Clinical Pharmacology

Study RB-FVIIa-006-13, the Phase 3 trial evaluating efficacy and safety of SEVENFACT manufactured using Process A and the scaled-up manufacturing process, Process B. Furthermore, few bleeding events in both dose arms were treated with products manufactured from Process B and Process A to achieve the target dose. To demonstrate comparability of the products manufactured using the two processes, PK assessments were performed in 14 patients. With the 225 mcg/kg dose, there were substantial differences in the PK analysis between the product manufactured under the two processes. As compared to the 75 mcg/kg dose, the 225 mcg/kg dose was associated with higher Cmax and AUC. The root cause has yet to be confirmed but inconsistencies in the potency assay and/or differences in the activity of the product are being considered. A recommendation for additional root cause analyses is planned in the regulatory action package and communication to the Applicant. For additional details please refer to the clinical pharmacology review memo. For details of the safety analysis of the sub-group that received the target dose of 225 mcg/kg using products manufactured through Process A and B, please refer to the Section 6.

4 4 1 MECHANISM OF ACTION

SEVENFACT is a recombinant human coagulation FVIIa of vitamin K dependent family of coagulation factors. In the presence of both calcium and phospholipids , FVII/FVIIa forms a complex with tissue factor (TF) and can activate FX to FXa directly, bypassing FIX or FVIII steps in the coagulation cascade. Activation of

Factor X to Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin. Thrombin converts fibrinogen to fibrin, which is critical for clot formation.

4.4.2 HUMAN PHARMACODYNAMICS (PD)

The pharmacodynamic efficacy of LR 796 was assessed using thrombin generation test with platelets (TGT), prothrombin time, rotational thromboelastometry (including maximal clot firmness) and activated PTT in the Phase 1 trial with hemophilia subjects with or without inhibitors. Three doses, 25mcg/kg, 75mcg/kg and 225 mcg/kg, were evaluated in the study; however, each subject was exposed to 2 doses in an ascending fashion.

The thrombin generation test with platelets is representative of the mode of action of Factor VIIa. A dose dependent effect was noted for area under the peak for thrombin generation with maximal effect observed for 225 mcg/kg dose followed by 75 mcg/kg and then 25 mcg/kg dose.

A reduction in prothrombin time and Activated Partial Thromboplastin Time was observed for all three doses, with the greatest reduction being noted with 225 mcg/kg, 75 mcg/kg and 25 mcg/kg in that order respectively.

Maximal clot firmness (MCF) assessed 5 minutes post infusion revealed dose dependent effects, with greater MCF noted with 225 mcg/kg dosing compared to 25 mcg/kg and 75 mcg/kg dosing,

Prothrombin fragments 1+2, d-dimers, and thrombin-antithrombin complex can indicate the risk of thrombosis by exaggerated pharmacodynamic effect of recombinant Factor VIIa. These were assessed during the Phase1 trial. For further details see Section 6.1.12.6. .

Thus, based on the dose dependent pharmacodynamic effects, the dose of 225 and 75 mcg/kg were selected for further evaluation in the Phase 3 study. The approach to examine two doses in a Phase 3 study is reasonable, and if found effective, may present two dose options for prescribers. Physician discretion, possibly depending on the site or severity of bleeding may factor into dose selection (for example, higher dose may be utilized for major bleeding episodes).

4.4.3 HUMAN PHARMACOKINETICS (PK)

Pharmacokinetics of SEVENFACT were assessed during the Phase 1 and Phase 3 trials.

During the Phase1 trial, PK assessments were collected prior to dosing and at multiple time points, up to 24-36 hours after drug administration in 15 subjects. Pharmacokinetic parameters were evaluated for 3 dose levels, 25 mcg/kg, 75

mcg/kg and 225 mcg/kg. The Cmax and exposure increased in a dose dependent fashion.

The half-life of SEVENFACT was approximately 2 hours with all doses. Per the Applicant, the PK-PD modeling indicated that time to reach effective coagulation levels of FVIIa occurs earlier with higher doses of Sevenfact Maximal clotting effect of Sevenfact was achieved at plasma concentration of 1500ng/ml. This was the basis for the Applicant's plan to evaluate two doses, 75 and 225 mcg/kg, in the Phase 3 study.

The Phase 3 trial compared PK parameters following administration of study product manufactured by Process A (small scale) vs Process B (large scale).The change from Process A to Process B was done as larger scale manufacturing was introduced during the study and approximately 30% of the bleeding events were treated with Process B product. A total of 14 subjects (7 in each arm) participated in the PK portion of the study. Higher Cmax and AUC were noted with the 225 mcg/kg dose with the Process B product as compared to the Process A product. This is summarized in table below.

Table 4: Pharmacokinetic results

Study No. RB-FVIIa-06-013 Dose: 225 µg/kg BW									
Parameter (units)	**Process A**				**Process B**				**T/R**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
Cmax (ng/ml)	1392.15	29.97	895	2039	2440.60	22.15	1629	3057	0.57
AUC0-t (hr*ng/ml)	1995.95	26.00	1365.99	3015.70	2784.59	20.03	2132.86	3331.12	0.72
AUC∞ (hr*ng/ml)	2032.25	25.80	1406.84	3063.37	2820.96	19.83	2161.95	3355.00	0.72

Two adolescent subjects b) (6) wo recived the 75 mcg/kg dose participated in the PK analysis. With process A , no difference was seen in the PK profile between them and adult subjects. For process B, the PK profile of the two adolescent subjects indicated high variance in PK profiles compared to adults; however, due to potency assay issues and small sample size, no conclusions can be drawn at this time.

The root cause of these discrepancies in the PK results at the 225 mcg/kg dose is unclear. Per the CMC reviewer, the differences between the two-manufacturing processes are unlikely to contribute to this observation. Errors related to stability testing and differences in potency assays are being evaluated. Thus, the safety and dose recommendations should be interpreted in the context of the potential difference in the potency assay.

4.5 Statistical

There is overall concurrence between the findings of the statistical and clinical reviewers. The statistical reviewer confirmed the efficacy of the product. Additionally, the statistical reviewer re-analyzed the primary efficacy endpoint based on clinical reviewer's assessment of bleed outcomes with re-adjudication of 15 bleed outcomes. Despite the re-adjudication, the primary efficacy endpoint met its success threshold. The secondary endpoint analyses provided by the Applicant were verified by the statistical reviewer. The results of the efficacy analysis based on the re-adjudicated outcomes will be the results that will be included in Section 14 of the label at the time of marketing approval.

4.6 Pharmacovigilance

Important potential risks with Sevenfact include immunogenicity to Factor VII and thromboembolic events. The clinical data submitted in the BLA did not identify any thromboembolic events or immunogenicity. The validation of the immunogenicity testing is being evaluated by CMC review division and barring any new requirement from CMC to re-test the samples, the clinical reviewer has not identified safety issues either based on the review of the two clinical studies, data from related class of products or based on the recommendations of the toxicology reviewer that would require a post-marketing study.

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

The data included in the clinical review of the submission include two studies that were submitted in Module 5 of this BLA. These studies are described below in Section 5.2

5.1 Review Strategy

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

Documents pertinent to this review are provided in 125641/0 and IND 15813. The pertinent sections BLA include sections 2.5, 2.7 and 5.3.5 and 5.3.6. Datasets related to RB-FVIIa-006-13 were reviewed for efficacy and safety, and datasets from the Phase 1 trial GTC –FVIIa-005-11 were reviewed for safety.

5.3 Table of Studies/Clinical Trials

Two clinical studies were reviewed in support of the efficacy and/or safety of rVIIa as per Table 5 below.

Table 5: Clinical Studies

Study Identifier/ Location of Study Report	Study Objectives	Study design	Dose	Number of Patients	Manufacturing Process
Phase 1b GTC-FVIIa-005-11 Section 5.3.4.2	PK/PD in adult patients > 18 years old with haemophilia A and B with or without inhibitors in a non-bleeding state	Multicenter, open-label, single-dose, dose escalation	25 µg/kg IV	10[1]	A (small scale)
			75 µg/kg IV	10[1]	
			225µg/kg IV	10[1]	

Source- BLA 125641/0 ,Module 2.7.2; Overview of Clinical Pharmacology Studies of SEVENFACT,Page 8.

Study ID (Location in BLA)	Total study sites, Locations	Study start, Status, Patients enrolled (Bleeding Episodes)	Design, Control type	Objectives, Primary endpoints	Study drug, Route & regimen	Gender, Median age (range)	Diagnosis, Inclusion criteria
RB-FVIIa-006-13, PERSEPT 1 (Clinical Study Report RB-FVIIa-006-13, Module 5.3.5.1)	Sites: 11 Bulgaria: 1 Georgia: 1 Poland: 1 Russia: 2 Ukraine: 2 UK: 1 USA: 3	29 Apr 2014 Completed 31 Jul 2015 25 planned, 27 enrolled (468 [465 mild/moderate; 3 severe])	Phase 3, multicenter, randomized, open-label, crossover study of 2 treatment regimens for bleeding episodes At least 22 patients were followed for ≥6 months until ≥352 bleeding episodes recorded Objective performance criteria	Efficacy, safety, PK, immunogenicity, healthcare resource utilization	LR769 75 or 225 µg/kg; ≤2 minute IV bolus infusion; then single injection per dose Phase A: Initial dose for safety and PK Phase B: Treatment of bleeding episodes, repeated PK	Male only 31.0 years (12-54)	Hemophilia A or B with inhibitors to FVIII or FIX Adults and adolescents, ≥12 years to 75 years

Source BLA 125641/0 , Module 2.7.3;Clinical Efficacy Study of SEVENFACT.Page 7.

Although studies GTC-FVIIa-005-11 and RB-FVIIa-006-13 were included in the safety analysis, a pooled analysis could not be performed as the dosing frequency and the doses in this study were different from Study RB-FVIIa-006-13.

5.4 Consultations

Not Applicable

5.4.1 ADVISORY COMMITTEE MEETING

An Advisory Committee Meeting was not convened for the discussion of this submission.

5.4.2 EXTERNAL CONSULTS/COLLABORATIONS

External consultations were not obtained.

5.5 Literature Reviewed

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6. Discussion of Individual Studies/Clinical Trials

6.1 Trial #1 – RB-FVIIa-006-13

A Phase III Study on the Safety, Pharmacokinetics, and Efficacy of Coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B Patients with Inhibitors to Factor VIII or IX.

The study was opened to enrollment on April 14, 2014 and was closed on July 31, 2015.

6.1.1 Objectives

-The primary objective was to assess the:

-efficacy of two separate dose regimens (75 mcg/kg and 225 mcg/kg) of SEVENFACT for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII (FVIII) or factor IX (FIX)

- safety of SEVENFACT (including the immunogenic potential of the drug product).

-The secondary objective was **t**o assess the pharmacokinetics (PK) of SEVENFACT (from both Process A and Process B) in hemophilia A or B patients with inhibitors to FVIII or FIX, without a current bleeding episode.

6.1.2 DESIGN OVERVIEW

The study is a global Phase 3, prospective, open-label, randomized, crossover study. Subjects were randomized to one of two doses (75 mcg/kg or 225 mcg/kg dose). In Phase A, the primary objective was to evaluate the safety of one dose of SEVENFACT. A subset of patients in Phase A were also to be included in the PK analysis following administration of a single infusion at the assigned dose. Subjects then entered the cross-over phase, Phase B, treated for bleeding episodes beginning with the dose they were randomized to, followed by cross-over to the alternate dose every 3 months unit the end of the study.Thus subjects received treatment for one of two doses for 6 months each.

Mild/moderate bleeding events were treated at home by subjects or caregivers. Treatment was to be initiated as soon as possible but within 4 hours of the first symptom of bleeding. Subjects with severe bleeding could receive the first dose at home, but required hospitalization for management of the bleeding episode thereafter.

Efficacy assessment included a combination of response assessments based on the 4-point hemostatic efficacy scale, need for other hemostatic or blood products, need for ongoing treatment with study drug and pain status 12 hours after study drug administration.

In July 2014, changes to manufacturing of the product to initiate (b) (4) process manufacturing (Process B) was introduced. These changes occurred during the Phase 3 study. At the FDA's request, PK characteristics were compared between drug product manufactured from original process (Process A) and process B (scaled up process), in 14 subjects

Reviewer's Comments-
1. This trial design included home based treatment of bleeding events in hemophilia subjects with inhibitors. This allows for early initiation of treatment avoiding long term sequelae of bleeding and improved convenience and quality of life.
2. The open label nature of this trial and response determination of treatment by patients could potentially lead to overestimation of the clinical benefit of the higher dose compared to the lower dose arm due to patient bias.

3. There is no expected cross over effect due to the short half-life of SEVENFACT and due to on demand treatment of bleeding events. The overall design of the trial is acceptable.
4. The exclusion of severe bleeding events from primary efficacy analysis limits the applicability of the results of efficacy to mild and moderate bleeding events.
5. To minimize risk of exposure of subjects with severe bleeding events to an ineffective therapy, the protocol required the Data Monitoring Committee to evaluate the activity of SEVENFACT for the treatment of mild and moderate bleeding events. If the preliminary evidence of activity was determined to be satisfactory, treatment of severe bleeding with SEVENFACT was allowed.

6.1.3 POPULATION

Key Inclusion Criteria-
Congenital hemophilia A or B of any severity and have one of the following:

- A positive inhibitor test BU ≥ 5 OR BU <5 but expected to have a high anamnestic response to FVIII or FIX or BU < 5 but expected to be refractory to increased dosing of FVIII or FIX, as demonstrated from the patient's medical history, precluding the use of FVIII or FIX products to treat bleedings
- 12 years or older, up to and including 75 years of age
- Required to have at least 3 bleeding episodes of any severity in the past 6 months
- Severe bleeding events were only included in the study after DMC review of treatment and efficacy of first 20 mild/moderate bleeding events. Severity of bleeding events was based on location, severity of symptoms and severity of trauma in cause of traumatic bleeding events. (For definition of bleeding events based on severity, see Appendix A).
- Patients on Immune Tolerance Induction (ITI) therapy

Key Exclusion Criteria
Patients who met any of the following criteria were excluded from the study:
1. Any coagulation disorder other than hemophilia A or B
2 Immuno-suppression (i.e., the patient should not have received systemic immunosuppressive medication, CD4 counts at screening should have been >200/μL)
3. Known allergy or hypersensitivity to rabbits
4. Platelet count <100,000/mL
5. Clinically relevant hepatic disease (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] >3 times the upper limit of normal) and/or renal impairment (creatinine >2 times the upper limit of normal)
6. History of arterial and/or venous thromboembolic events (such as myocardial infarction, ischemic strokes, transient ischemic attacks, deep venous thrombosis [DVT] or pulmonary embolism [PE]) within 2 years prior to first dose of study drug, or current New York Heart Association (NYHA) functional classification score of stage II –IV

Reviewer's Comments-

The study included subjects with low titer inhibitors expected to have high anamnestic response to Factor VIII or IX. The inclusion criteria does not specify the threshold of Factor VIII inhibitor titer upon exposure to factor products that would constitute an anamnestic response. Anamnestic response can diminish over time and the selection criteria as described can introduce selection bias by inclusion of subjects with a lower risk (decreased severity and frequency of bleeding) in the trial. However, the activity of Factor VIIa in the hemostatic response is expected to be similar to those subjects who have high titer inhibitors at study entry as LR 796 is expected to bypass Factor VIII and IX leading to thrombin generation.

The inclusion and exclusion criteria were considered acceptable.

6.1.4 STUDY TREATMENTS OR AGENTS MANDATED BY THE PROTOCOL

SEVENFACT was presented as a lyophilized powder in single use vials containing 1, b) (4) 5 mg coagulation factor VIIa (recombinant). After reconstitution with sterile water, each ml contained 1 mg of factor VIIa. This was administered over 2 minutes as an IV bolus.

All subjects enrolled in the trial received a single IV administration of SEVENFACT at a dose of 75 mcg/kg or 225 mcg/kg depending on the randomization during treatment Phase A.

During Phase B, subjects were treated with either 75 mcg/kg or 225 mcg/kg dose of SEVENFACT depending on the randomization as per the dosing regimen described below and based on the severity of bleeding events.

Mild/moderate bleeding events

- A 75 mcg/kg was followed 9 hours later with 75 mcg/kg dose if the hemostatic response to treatment was unsatisfactory. 75 mcg/kg could be repeated, if needed, every 3 hours(up to and including 21 hours after the first administration) until the bleeding episose was successfully treated. A maximum of six treatments in total were allowed in this treatment regimen for mild/moderate bleeding events.
- A 225 mcg/kg dose was followed 9 hours later with 75 mcg/kg dose if the hemostatic response to treatment was unsatisfactory. The 75 mcg/kg dose could be repeated, if needed, every 3 hours (up to and including 21 hours after the first administration) until the bleeding episode was successfully treated. A maximum of 6 treatments in total were allowed in this treatment regimen for mild/moderate bleeding episodes.

- For both treatment regimens, if bleeding was not successfully treated as assessed at 24 hours after first drug administration then treatment with SEVENFACT was discontinued and alternative treatment was given.
- Treatment with antifibrinolytics (e.g. tranexamic acid and aminocaproic acid) were allowed on the study.
- Lot numbers of SEVENFACT used were A3C05, A3C06, A3C07, A3C08, and A4C01.

Severe bleeding

- A 75 mcg/kg dose, repeated every 2 hours until improvement in bleeding was observed. The frequency of dosing was then changed to every 3 hours for 1-2 days and then increased to 4-12 hours depending on the type of bleeding for as long as needed.
- 225 mcg/kg dose could be followed 6 hours later with dose of 75 mcg/kg and then repeated every 2 hours until improvement in bleed was observed after which the interval was increased to 3 hours for 1-2 days and then 4-12 hours for as long as needed.

6.1.5 DIRECTIONS FOR USE

SEVENFACT is provided in a kit which contains syringe plunger rod, prefilled syringe with diluent, vial adapter (1 mg, (b) (4) and 5 mg) and drug vial with lyophilized drug powder. The drug powder is reconstituted with diluent and must be used within 4 hours of reconstitution.

Reviewer's Comments- This is a combination product as it is co-packaged with in a convenience kit. A consult review by CDRH was not requested as individual parts of kit are cleared under 510k approval pathway. The syringe plunger, rod, prefilled syringe with diluent and vial adapter are commonly used with other biological products and so separate approval was not considered necessary per the CMC review team.

6.1.6 SITES AND CENTERS

Patients were screened at 13 study sites.: Belarus (1 site; Site 17), Bulgaria (1 site; Site 10), Georgia (1 site; Site 12), Israel (1 site; Site 07), Poland (1 site; Site 23),Russia (2 sites; Sites 01 and 15), United Kingdom (1 site; Site 13), Ukraine (2 sites; Sites 11and 26), and United States ([US] 3 sites; Sites 04, 19, and 20).

Two patients at sites in Belarus and Israel were screened but did not meet eligibility criteria.

Four other sites were activated, but did not screen any patients: Romania (1 site; Site 24), Russia (1 site; Site 06), US (2 sites; Sites 21 and 27).

Therefore, 11 sites randomized 27 patients.

6 1 7 SURVEILLANCE/MONITORING

Study procedures and monitoring schedule is outlined in Table 6 below.

Table 6 : Monitoring Schedule

PHASE A – INITIAL PHASE

Evaluation	Screening Days -21 to-1	Predose	0 min	10 ± 2 min	30 ± 5 min	1 hour ±10 min	2 hours ±10 min	PK Patients 4 hours ±10 min	PK Patients 8 hours ±10 min
Informed Consent	X								
Inclusion and Exclusion Criteria	X	X							
Demographics/Medical History	X								
Physical Examination[1]	X	X							
Clinical Laboratory Tests and Urinalysis[2]	X								
Vital Signs	X	X			X	X	X	X[3]	X[3]
Electrocardiogram	X								
Randomization		X							
Drug Administration			X						
Concomitant Medication Assessment	X	X							
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Pharmacokinetic (PK) Assessments[3]		X		X	X	X	X	X	X
Immunogenicity[4]		X							

PHASE B -TREATMENT OF MILD/MODERATE BLEEDING EPISODES

	Mild-Moderate Bleeding Episode									
Evaluation	Pre-treatment	0 min	3 hrs	6 hrs	9 hrs	12 hrs	15 hrs	18 hrs	21 hrs	24 hrs
Bleeding Characteristics[1]	X									
Drug Administration[2]		X	X[3]	X[3]	X	X	X	X	X	
Efficacy assessment[4]			X	X	X	X[5]	X	X	X	X[5]
Patient Diary	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X

The assessments of efficacy, adverse events and concomitant medications were made by subjects and caregivers at different time points as provided below.

SCHEDULE OF EVENTS (PHASE B: FOLLOW-UP VISITS)

	Following treatment in Phase A					Following 24 weeks visit		
Evaluation	**3 wks ±2 days**	**6 wks ±5 days**	**12 wks ±5 days**	**18 wks ±5 days**	**24 wks ±5 days**	**Every 6 wks ±5 days**	**Every 12 wks ±5 days**	**End of Study/Early Termination Visit**
Physical Examination[1]	X[4]	X[4]	X[4]		X		X[4]	X
Safety Lab Tests								
Hematology, Chemistry, Urinalysis		X	X		X		X	X
Coagulation (Central and Local Lab)			X[3]		X		X[3]	X
Adverse Event Assessment	Throughout Study							
Weight			X		X		X	
Vital Signs	X	X	X	X	X	X	X	X
Electrocardiogram		X	X		X			X
Healthcare Resource Utilization			X		X		X	X
Concomitant Medication Assessment	Throughout Study							
Check Drug Accountability and Patient Diary	X[5]	X	X	X	X	X	X	X
Immunogenicity	X	X	X	X	X	X	X	X[2]

Source: Adapted form CSR Persept I, Table 5, Pages 51-54.

The follow up visits were conducted at the hospital/hemophilia treatment center by study site staff. Site staff also contacted subjects weekly to confirm subjects' compliance with study treatment and collect information about bleeding episodes, adverse events etc.

Development of thrombotic events, acute allergic reaction to the study drug or neutralizing antibody to SEVENFACT would lead to treatment cessation. Patient could be withdrawn from the study for protocol violations that rendered the data uninterpretable, for patient safety reasons or upon patient request.

Data Monitoring Committee (DMC)

-During the conduct of the trial, the DMC met on a quarterly basis for review of the study data. The DMC also reviewed the following-
- Study data after treatment of 20 mild/moderate bleeding events to make a decision regarding inclusion of severe bleeding events in the study
-Efficacy data following treatment of 60 mild/moderate bleeding events prior to initiating the pediatric and surgical trials with the study drug.
-The Interim primary efficacy analysis for 80% (252) bleeding events for the purpose of sample size re-estimation

6 1 8 ENDPOINTS AND CRITERIA FOR STUDY SUCCESS

Time to clinical response of bleeding event is an indicator of efficacy as faster onset of action of SEVENFACT is associated with increased rate of thrombin generation and shorter time to bleeding cessation. Control of bleeding at an earlier time point is expected to minimize long term joint and cartilage destruction associated with joint bleeding events. The primary efficacy end point was the successful treatment of mild/moderate bleeding episodes at 12 hours after the first administration of SEVENFACT. Successful treatment of bleeding episode required that all of the criteria outlined below were met.

• "Good" or "Excellent" response noted by the patient using a 4- point hemostatic efficacy scale.
• 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 that would indicate continuation of bleeding beyond time point
• No increase of pain beyond time point (12 hours) that could not otherwise be explained.

The 4 - point hemostatic efficacy scale used for patient assessment of response to treatment is noted below.

Table 7: 4-point efficacy scale

Response	Description
None	No noticeable effect of the treatment on the bleed or worsening of patient's condition. Continuation of treatment with the study drug was needed.
Moderate	Some effect of the treatment on the bleed was noticed, e.g., pain decreased or bleeding signs improved, but bleed continued and required continued treatment with the study drug.
Good	Symptoms of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal haemorrhage) had largely been reduced by the treatment, but had not completely disappeared. Symptoms had improved enough to not require more infusions of the study drug.
Excellent	Full relief of pain and cessation of objective signs of bleed (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal haemorrhage). No additional infusion of study drug was required.

Source: (Amby, 2009)

Source: Adapted form CSR Persept I, Table 5, Page 44.

Pain was assessed and rated using the Visual Analogue Scale (VAS) by the patient.

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

The first amendment of the protocol (12/5/2013) changed the primary endpoint of the study from success per patient to proportion of success of all bleeding episodes.

Criteria for study success-

The primary efficacy analysis was to compare the proportion of successfully treated bleeding episodes in each of the two treatment arms with the pre-specified objective performance criterion (OPC). An OPC of 55% was determined based upon the reported success of treatment with bypassing agents in literature.

The protocol specified success was defined as statistically significant higher success compared to OPC. The study was powered to detect a 15% improvement over OPC for each of the two treatment arms with 80% power with 0.0125 type 1 error.

Reviewer's Comments-

The primary efficacy endpoint evaluation was comprised of 5 components that included the 4-point hemostatic scale.
The hemostatic scale incorporates assessment of symptoms associated with bleeding namely swelling, tenderness, decreased range of motion and pain. The 4-point scale includes assessment of symptoms such as swelling, range of motion and tenderness; however, these parameters were not recorded. The 4-point scale also assesses for requirement for continued treatment at the 12 hour time point. However, since the majority of the bleeding events were mild to moderate in severity, these bleeding events tend to be self-limited. Thus, the utility of the requirement of continued treatment in mild to moderate bleeding events is questionable. Thus for assessment purposes, the 4- point scale relied primarily on pain for assessment outcomes in subjects with mild to moderate bleeding. In addition, the use of "some effect of treatment on the bleed "and "symptoms of bleed largely reduced" in definition of "moderate" and "good" respectively are vague and lack objectivity.Thus, objective assessment methods are limited and the hemostatic efficacy assessments rely on more subjective assessment such as pain, range of motion and swelling which have inherent subjectivity aspects. Thus, assessment of hemostatic responses are challenging when the assessments are restricted to mild-moderately severe bleeding episodes and target tissues are predominantly joints and soft tissue. Nevertheless, these efficacy parameters and bleeding sites have been typically used in the assessment of hemostatic response for hemophilia A and B. In addition, in this study, concomitant analgesics were permitted during the efficacy assessment and control of pain was a major criterion in the efficacy assessment. Thus, the concomitant use of analgesics interferes with the efficacy assessment. To minimize bias, in the IND phase, the clinical reviewer communicated with the Applicant that hemostatic rating scale should be revised to include more objective criteria to assess response by including the number of infusions required to treat a bleed, time frame over which bleed resolves completely and time to pain relief. The sponsor was also informed that in the absence of objective measures, the assessment of primary efficacy endpoint would be a review issue. In response to this FDA advice, the sponsor stated that the definition of patient assessment are inherently vague as signs and symptoms of

joint and soft tissue bleeding events are difficult to quantify and can be subjective. No change to the hemostatic scale was made and additional objective assessment criteria were not included. Therefore, the review of the efficacy focused on the quality of data collected for pain assessment to ensure reliable assessments were performed, evaluation of confounding by concomitant analgesic use and evaluation of hemostatic efficacy in severe bleeding. Thus, the final efficacy analysis based on readjudication of the outcomes is considered satisfactory to determine efficacy.

To enhance the robustness of the efficacy analysis, the Applicant was advised by the clinical reviewer to include severe bleeding events in the primary efficacy assessment. Based on FDA's advice, additional sensitivity analyses were performed on the primary and secondary efficacy analysis that included efficacy assessment of severe bleeding events. However, severe bleeding events are uncommon in the eligible population.

Secondary end points-
Time to clinical response of bleeding event is an indicator of efficacy as faster onset of action of SEVENFACT is associated with increased rate of thrombin generation and shorter time to bleeding cessation. Control of bleeding at an earlier time point is expected to minimize long term joint and cartilage destruction associated with joint bleeding events. This efficacy end point is confounded by the open label, non-controlled study design and use of concomitant pain medications in the study. Fewer administrations of drug are also supportive of drug efficacy and will be of value to subjects with limited venous access with improved convenience.
Overall the secondary end points are clinically relevant and lend support to the primary efficacy analysis.

6.1.9 STATISTICAL CONSIDERATIONS & STATISTICAL ANALYSIS PLAN

Analysis of Primary Efficacy Endpoint

The proportion of mild/moderate bleeding episodes treated with each dose of SEVENFACT that were classified as being successfully treated were compared with objective performance criterion (OPC) of 0.55.The protocol specified success was defined as statistically significant higher success compared to OPC. The study was not powered for statistical comparison between the two dose arms.
The null hypothesis for the primary efficacy endpoint was $p \leq 0.55$ where p is proportion of successfully treated mild and moderate bleeding events at 12 hours. The null hypothesis was tested using a one-sided, one- sample, normal approximation test taking into account the correlation between bleeding episodes for a given subject. The test was conducted to account for multiplicity with a type

1 error of 0.0125. Proportion of successes was presented with 95% CI for the true proportion.

No imputation of the missing data was performed for the analysis of primary efficacy endpoint. A sensitivity analysis was performed to examine the effect of missing data on the primary efficacy endpoint.

Reviewer's Comments
Clinical trials evaluating efficacy of bypassing agents in bleeding subjects with inhibitors have evaluated efficacy ranging from 6 hours to 48 hours after study drug administration. The primary efficacy evaluation at 12 hours in this study is reasonable; however, some mild and moderate joint bleeding events may be self-limited. A preferred endpoint assessment based on assessments performed at a time interval of less than 12 hours (for example, 6 or 8 hours following the administration of SEVENFACT would have been more relevant for assessment of efficacy in patients with mild/moderate bleeding.

Analysis of Secondary Efficacy Endpoint-

- The proportion of mild/moderate bleedings with good or excellent response as reported by the patient was analyzed. Additional sensitivity analyses were not performed based on the FDA re-adjudicated assessments (please see Summary of Protocol Violations) as was done with the primary efficacy assessments.
- The time to patient assessment of good or excellent response of mild/moderate bleeding episodes was analyzed at the bleeding episode level using Kaplan-Meier method. A cox proportional hazards regression model was used to test for difference in hazard ratios between the 2 treatments.
- The number of administrations and total amount of study drug administered per bleeding episode was summarized on bleeding episode level by actual treatment regimen. A comparison of the means in two treatment arms was performed.

Sample Size Determination-
With a true proportion of success of 0.70, a correlation among bleeding episodes for a given patient of 0.1 and an OPC of 0.55, a sample size of 22 subjects and 352 bleeding episodes (assuming 8 bleeding events/per regimen/patient) provided a statistical power of ≥ 80%. The study plan was to enroll 25 subjects to account for drop outs and unevaluable bleeding events. The original protocol required 10 severe bleeding events before the end of the study. However, the protocol was revised to remove this requirement with the Applicant's justification that severe bleeding events were uncommon in patients with hemophilia A and B.

Reviewer's Comments
During the study, the protocol was amended to modify the primary endpoint from success per patient to proportion of success for all bleeding episodes.

We agree with this change as every subject is expected to have multiple bleeding events of varying severity. Management and outcome of each bleed in a subject may be different and thereby complicates a patient specific analysis.

6.1.10 STUDY POPULATION AND DISPOSITION-

6.1.10.1 Populations Enrolled/Analyzed

All analysis of efficacy and safety was performed on subjects that were treated. ITT analysis was not planned for primary efficacy endpoint. However, all 27 subjects randomized were included in efficacy and safety analysis. Although the treated population was the primary efficacy analysis population, all randomized subjects received at least one dose of treatment. Thus the ITT population and treated population are the same.

Intent to Treat population (ITT) is defined as all subjects that were randomized.

Enrolled Population was defined as all patients who signed an informed consent. Analyses of non-treatment emergent adverse events were performed on this population.

Safety Population was defined as all enrolled patients who received at least 1 dose of study drug. All safety endpoints and baseline characteristics were analyzed on this population.

Reviewer's Comments-
Thromboembolism is expected adverse event with the class of recombinant Factor VIIa . Subjects with thrombophilia and vasculopathy were excluded. Thus, the safety of SEVENFACT in this population is unknown.

The Treated population was defined as all enrolled patients who received at least one study drug administration to treat a bleeding episode during Phase B of study.

Primary Efficacy analyses were performed based on the treated Population.

The Evaluable PK population (hereafter referred to as the PK population) was defined as all treated patients who had post-study drug administration FVIIa activity levels determined.

The definition of treated and safety population outlined in the protocol is appropriate for safety and efficacy assessment in this clinical trial.

6.1.10.1.1 Demographics
Table 9 below summarizes the demographic characterisics of the study population.

Table 8: Demographic characteristics of the Enrolled Population

Parameter	Statistics	Treatment Regimen at Randomization		Overall (N=27)
		75 µg/kg (N=13)	225 µg/kg (N=14)	
Age (years)	Mean (SD)	31.8 (12.10)	30.1 (12.98)	31.0 (12.35)
	Median	31.0	30.5	31.0
	Minimum/Maximum	13/51	12/54	12/54
Age categorized [n (%)]	12-18 years	2 (15.4%)	3 (21.4%)	5 (18.5%)
	≥18 years	11 (84.6%)	11 (78.6%)	22 (81.5%)
Race [n (%)]	Asian	1 (7.7%)	0 (0.0%)	1 (3.7%)
	Black or African American	0	1 (7.1%)	1 (3.7%)
	White	12 (92.3%)	13 (92.9%)	25 (92.6%)
Ethnicity [n (%)]	Hispanic or Latino	1 (7.7%)	0	1 (3.7%)
	Not Hispanic or Latino	12 (92.3%)	14 (100%)	26 (96.3%)

Source: Adapted from CSR Persept I, Table 9. Page 84

Reviewer comments: The median age of the population is consistent with trials that enroll subjects with inhibitors to FVIII and FIX. The age, race and ethnicity were balanced between the two arms because of the cross over nature of the study.The study allowed subjects up to 75 years of age. However, the oldest subject enrolled in the study was 54 years of age. Thus the data regarding safety of this product in subjects who are 65 years and older is limited.
Older subjects are at higher risk for thrombotic events due to underlying comorbidities. This issue will need to be considered while extrapolating the data to older adults.

6.1.10.1.2 edical/Behavioral Characterization of the Enrolled Population

Although the study allowed subjects up to 75 years of age, the oldest subject enrolled was 54 years of age. The study excluded subjects with previous history of arterial or venous thromboembolic disease or heart failure within two years prior to study entry.

Two subjects randomized to the 75mcg/kg arm continued immune tolerance induction (ITI) therapy with Factor VIII products while in the study. A total of 99.3% (460/463) of bleeding events were treated at home.

Three severe bleeding events were treated, and all three bleeding events occurred in subjected randomized to the 225 mcg/kg arm. Severe bleeding events are not included in the primary efficacy analysis as pre-specified in the protocol.

Table 10 summarizes the baseline disease characterics of study subjects.

Table 9: Baseline Disease characteristics

Parameter	75mcg/kg N=13	225mcg/kg N=14	Overall N=27
Hemophilia A	13(100%)	12(85.7%)	25 (92.6%)
Hemophilia B	0	2 (14.3%	2 (7.4%)
Moderate hemophilia	1 (7.7%)	1 (7.1%)	2 (7.4%)
Severe hemophilia	12 (2.3%)	13 (92.9%)	25 (92.6%)
Inhibitor Status (BU <5)	7(53.8%)	6 (42.9%)	13 (48.1%)
Inhibitor Status BU ≥ 5	6 (46.2%)	8 (57.1%)	14 (51.95)
Mean # of bleeding events 6 months prior to study entry (range)	14.5 (3,50)	11 (3,24)	12.7 (3, 50)
Target Joints	9 (69.2%)	8 (57%)	17 (63%)

*Of the 13 subjects with low titer inhibitor, 11 (85%) were expected to have high anamnestic response to Factor VIII or Factor IX and two (15%) were expected to be refractory to Factor VIII or IX therapy.

Table 10: Characteristics of the Bleeding Events

Type of Bleed		
Spontaneous	379	81.8%
Traumatic	84	18%
Unclassified	2	0.04%
Site of Bleed		

Joint	395	85.3%
Soft Tissue	22	5%
Oral/Nasal	25	5.4%
Others	21	4.5%
Time to Treatment		
<60 mts	392	84.6%
>60 mts	71	15.3%
Target Joint Bleeding events		
Yes	135	29%
No	328	70.7%
Severity of Bleed		
Mild	99	12%
Moderate	366	78%

Reviewer's comments

The baseline bleeding history is similar to a study conducted by Key Nigel et. al. (Thombo Hemost 1998), who evaluated the efficacy and safety of home treatment with NovoSeven in hemophiliacs with inhibitors. Study RB-FVIIa-006-13 enrolled subjects with a history of ≥ 2 mild-moderate bleeding events 12 months prior to study enrollment. Of the 876 bleeding events evaluated in this study, only 6 bleeding events were severe .

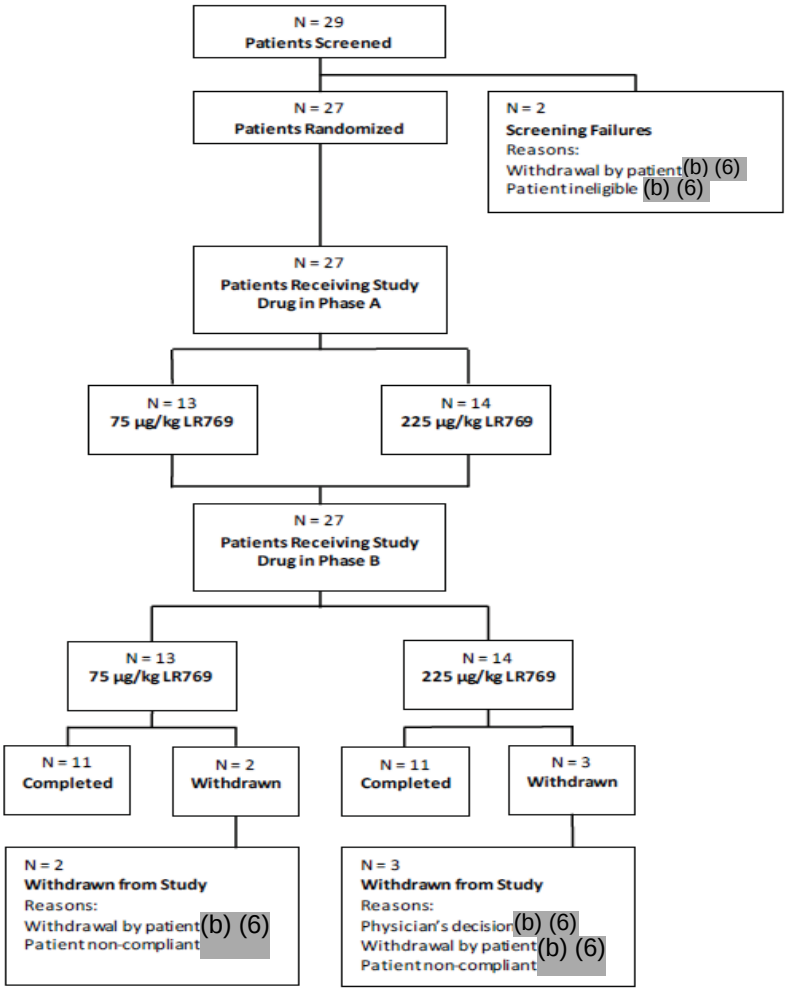
In comparison,RB-FVIIa-006-13 (Study 1) enrolled higher risk subjects with history of at least 3 bleeding episodes in last 6 months. Majority of bleeding episodes were treated at home and within 60 minutes of the bleeding event. Thus, the inclusion of only three severe bleeding events in this study is consistent with the severity of bleeding events in the eligible population.

Overall, the characteristics of the patients and bleeding events are representative of real- world hemophilia population and lends external validity to the trial.

Subject Dispostion

Subject disposition is summarized in Figure 1 below.

Figure 1: Disposition of Patients



Adapted from BLA 125641 Clinical Study Report for protocol RBFVIIa-006-13, Page 77.

A total of 29 patients were screened. There were 2 screen failures, Subject (b) (6) withdrew prior to treatment at the patient's request and Subject b) (6) was considered ineligible.

Reason for subject withdrawal in the 75 mcg/kg arm

(b) (6)- withdrawal by patient as lower dose was considered ineffective by the patient
(b) (6)-patient was non-compliant and committed 99 major protocol violations.

Reason for subject withdrawal in the 225 mcg/kg arm
(b) (6)-non-compliance and difficulty administering study drug independently
(b) (6)-personal issues at home

(b) (6)-non-compliance; subject missed week 3 and week 6 visit and did not respond to call from investigator.

As noted in the figure above, 27 subjects were treated at least with one dose and represent the treated and safety population. Of the 27, 22 subjects completed the study, with 11 subjects in each arm.

The treated population and safety population included all 27 subjects. For primary efficacy analysis purposes, the analysis population is represented by subjects (n=27) who received one dose of treatment for a bleeding episode. A bleeding episode was considered evaluable if efficacy assessments were performed at the protocol specified 12 hours. Missing bleeding events were excluded in the analysis per the protocol specified analysis plan.

Reviewer's Comments-
None of the subject withdrawals from either dose arm were related to adverse events or safety issues.

Disposition of Bleeding Events per the Applicant
Total bleeding events in the study: 465
Evaluable bleeding events (Applicant's assessment): 443
Missing bleeding events – 22 (Applicant's assessment)

Reviewer's Comments-
A total of 22 out of 465 (4.7%) bleeding events were characterized as missing by the Applicant, as efficacy assessments at the 12-hour time point were unavailable. Per the FDA clinical reviewer, 5 out of 22 bleeding events were considered evaluable. These events were included in the efficacy analysis. The decision to include these five bleeding events was related to the availability of efficacy assessments including pain scores that were documented within 1 hour of the intended time point. In the reviewer's opinion, the deviation in the timing of the efficacy assessments are minor.

Table 11: Missing Bleeds Re-adjudicated by the FDA Clinical Reviewer as Success/Failure

Subject ID	Date of bleeding event	Location	Dose	FDA assessment
(b) (6)	(b) (6)	Rt. Knee	225 mcg/kg	Failure
(b) (6)	(b) (6)	Rt. elbow	225 mcg/kg	Failure
(b) (6)	(b) (6)	Left elbow	75 mcg/kg	Success

(b) (6)	(b) (6)	Left elbow	75 mcg/kg	Failure
(b) (6)	(b) (6)	Left ankle	75 mcg/kg	Success

*Efficacy assessment at 11 hours 20 minutes with moderate outcome.
^ Efficacy assessment was done at 11 hours and 5 minutes with no improvements in VAS pain score
# Efficacy assessment was done at 11 hours with VAS pain score improvement from 80 to 0.
** Efficacy assessment at 10 hours 55 minutes was excellent

Final Disposition for primary efficacy analysis of Bleeding Events per FDA assessment
Total bleeding events in the study: 465
Evaluable bleeding events (Reviewer's assessment): 448
Missing Bleeding events – (Reviewer's assessment): 17.

Protocol Violations

Summary of Major Protocol Violations

Table 12: Major Protocol Violations

Violation Category	Treatment Regimen at Randomization		Overall (N=27)
	75 µg/kg (N=13)	225 µg/kg (N=14)	
Number of patients with major violation	6	6	12
Number of major violations	123	17	140
Study procedure or assessment-related	64	7	71
Study medication[1]	58	8	66
Informed consent[2]	1	-	1
Other[3]	-	2	2

Source-BLA 125641/0, Clinical Study Report ;RB-FVIIa-006-13,Page 81.

Of the 140 major protocol violations in this study, 90 occurred from a single subject (b) (6) who was randomized to the 75mcg/kg arm. This patient did not record efficacy data in the patient dairy and infused study drug over longer time than the recommended infusion duration of 2 minutes. This subject was withdrawn from study due to non-compliance. Other major protocol violations were related to the dosing; subjects who were assessed to have moderate efficacy were to continue additional doses, but weren't administered the product and subjects with good hemostatic efficacy were administered the product.

Reviewer's Comments-
70% of major protocol violations were contributed by a single patient who was non-compliant with recording hemostatic responses and with duration of drug administration. The statistical analysis plan specified that subjects missing hemostatic assessments were not required to be included in the primary efficacy analysis. In summary, the protocol violations are not unexpected for home based, patient administered treatment regimen and did not affect the overall analysis of the efficacy in the study.

6.1.11 EFFICACY ANALYSES

6.1.11.1 nalyses of Primary Endpoint(s)

The primary efficacy analysis was performed on the treated population as specified in the protocol. This included all randomized 27 subjects.
Overall there were 465 mild/moderate bleeding episodes that occurred in 27 subjects. Overall, 17 bleeding events had missing data making them in-evaluable as hemostatic efficacy assessments at 12 hours were missing. There were 448 evaluable bleeding events. The primary efficacy analysis was performed without imputing missing values as was pre-specified in the protocol.

Table 13: Primary Efficacy Analysis Results

Dose administered	Success	Success proportion	95% CI (p value)	Failures	Missing	Total
75 mcg/kg	197	81.7%	72.3, 91.2 (p<0.001)	44	11	252
225 mcg/kg	188	90.8%	83.7; 98 (p<.001)	19	6	213
Total	385	85.9%	78.4-93.5 (p<.001)	63	17	465

The primary efficacy analysis demonstrates that treatment with both dosing regimens, 75 mcg/kg and 225 mcg/kg, resulted in treatment success and was considered statistically significant as compared to the OPC of 55% at an adjusted one-sided alpha of 0.0125.

During the review of the primary efficacy analysis of evaluable bleeding events, discrepancies were noted between the reviewer's and the Applicant's assessment of efficacy outcomes for 10 bleeding events. These discrepancies were the a) result of concomitant use of pain medications by patients during the efficacy observation period and b) exclusion of pain outcomes in the efficacy outcomes while relying solely on the hemostatic response. In the opinion of this reviewer, the use of concomitant pain medications confounds the interpretability

of the pain outcomes. Pain outcomes were a required component of the efficacy assessment and used in conjunction with the hemostatic response for primary efficacy analysis. Summary of discrepancies noted by the clinical reviewer is described below.

Re-adjudication of efficacy outcomes

Efficacy outcomes were re-adjudicated by the FDA clinical reviewer in several instances as described below. These re-adjudications were performed when the efficacy adjudications were inconsistent with the definition of efficacy outcomes. The majority of the discrepancies in the outcomes between the Applicant and the FDA reviewer were related to pain assessments and the confounding effects from the use of concomitant pain medications.

Re-adjudication related to pain assessments
VAS pain scores were reviewed for all bleeding events designated as successfully treated.

-31 bleeding events with successful outcomes as per the Applicant were identified for further review and adjudication by the FDA reviewer. FDA review identified that the 31 patients experienced worse or unchanged pain based on the VAS score at 12 hours and compared to baseline. By protocol definition, ongoing pain without improvement is considered a failure. These were further reviewed for other supporting information.

- 5 out of 31 bleeding events involved joints and soft tissue and were classified as successful by the Applicant despite having worsening or unchanged pain score at 12 hours. These were designated as failures by the FDA clinical reviewer. (See table 17, Appendix A)

- 26 remaining bleeding events were reviewed. These bleeding events have baseline VAS scores of 0 that remained 0 at 12 hours, therefore, by definition were considered as unchanged pain score. Additional supportive efficacy assessments were reviewed.

    - 21 out of these 26 bleeding events had baseline VAS score of 0 and these were visible oral/nasal bleeding events. Since visible oral/ nasal bleeding events do not typically present with pain and success is apparent upon bleeding cessation, these were confirmed as successfully treated bleeding events. No further procedures/ interventions were needed for treatment of these bleeding events.
    - Five of the remaining bleeding events occurred in the soft tissue and joints and had baseline VAS pain score of 0

and 12-hour pain assessment of 0. These were counted as successful since no further treatment was administered beyond the 12 hour time point.

Re-adjudication related to confounding from concomitant pain medication use .

Since the primary efficacy end point of successful hemostasis was assessed primarily by pain, the use of concomitant analgesics and anti-inflammatory drugs while subjects were enrolled on the clinical trial was assessed. Concomitant anti-inflammatory drugs were allowed on the study. However, since improving pain score was main criteria for assessment of hemostatic efficacy, we identified 5 bleeding events with successful outcome where the concurrent use of analgesics/anti-inflammatory drugs could confound the assessment of pain score and hemostatic efficacy and designated them as failures. This did not include stable chronic use of pain medication or use of analgesics during the study but not in close proximity to occurrence of a bleed. Details of these bleeding events are outlined in Table 18, Appendix A.

Severe Bleeding Events
-Three severe bleeding events occurred during the study and all 3 were randomized and treated on the 225 mcg/kg arm. The severe bleeding events occurred in the right hip, soft tissue /muscle and renal bleed. Two episodes were occurred spontaneously and 1 was traumatic. All 3 episodes required hospitalization as specified in protocol.
-One subject was treated with three 225 mcg/kg doses of SEVENFACT which constituted major protocol violation. The remaining 2 subjects were treated with 1 and 5 doses of SEVENFACT respectively. All 3 severe bleeding events were treated successfully and this was accompanied by an improvement in VAS pain score.

Sensitivity analysis of primary efficacy end point was conducted to examine the effect of missing data. Bleeding events were considered missing if 12 hour efficacy assessment was not available. In general, the results of sensitivity analysis were consistent with those of main primary efficacy endpoint analysis. Please refer to Table 13 for the primary efficacy analysis results based on the re-adjudication of the efficacy outcomes.

6.1.11.2 Analyses of Secondary Endpoints

1. Proportion of mild/moderate bleeding episodes with a “good” or “excellent” patient reported assessment at 12 hours after initial study drug administration.

Overall 396/465 (85.2%) mild/moderate bleeding events had good or excellent responses noted at 12 hour time point. The observed proportions for each of the dosing arm are presented in Table below-

Table 14 Proportion of Bleeding events with Successful outcome Based on Patient Assessment

Dosing	Bleeding events with good/excellent outcome	P value
75mcg/kg	85.7%(95%CI 75-96.4)	<.001
225mcg/kg	93.7% (95%CI 88-98.6)	<.001

Source: FDA reviewer

2. Time to assessment of a "good" or "excellent" response of mild/moderate bleeding episodes by the patient.

The median time to "good" or "excellent" response was 5.98 hours (95%CI: 5.95, 6.00) for the 75mcg/kg dose arm and 3 hours (95% CI n/a) for 225 mcg/kg dose. This difference was statistically significant with p=.001.

3. Number of administrations and total amount of drug administered per mild/moderate bleeding episode. This is summarized below.

Table 15: Number of Doses and Mean Dose Administered Per Bleeding Episode

Dose	75mcg/kg N=25	225mcg/kg N=25	Overall N=27
Mean no. of doses (range)	2.5 (1-12)	1.4 (1-6)	2.0
Median no. of doses	2.0	1.0	1.0
Mean dose/ bleeding episode (mcg/kg)	187	252	217

Source: Adapted from the CSR Persept I.

Reviewer' Comments-

The results of the secondary analysis are concurrent with the overall conclusions from the primary analysis. The median and mean doses administered in the higher dose arm were less than the lower dose arm supportive of a dose response relationship.

6.1.11.3 Subpopulation Analyses

There were 5 subjects included in the trial that were 12-18 years of age and they contributed 79 bleeding events to the study. For these subjects, the proportion of successfully treated bleeding events was higher for both treatment regimens compared to main results of main primary efficacy analysis. For the 75 mcg/kg arm, the success rate was 95.3 %(95% CI; 84%-100%) and 94.3 %(95% CI;88%-100%) for 225 mcg/kg arm.

Reviewer's comment: The results are consistent with the primary efficacy findings with the caveat that the limited sample size precludes conclusions that the efficacy in adolescents is superior to that in adults.

6.1.11.4 Dropouts and/or Discontinuations

Five subjects were discontinued from the study during phase B. Please refer to 6.1.10 for details

Reviewer's Comments-
None of the subjects were discontinued from the study due to adverse events. Discontinuation from the study due to non-compliance was the major cause of study discontinuation.

6.1.11.5 Exploratory and Post Hoc Analyses
Not applicable

6.1.12 SAFETY ANALYSES

All 27 subjects were exposed to SEVENFACT and were included in the safety analysis.

6.1.12.1 Methods

For details of monitoring, please refer to Section 6.1.7
For analysis purposes, the safety population consists of subjects who received at least one dose of study drug. Adverse events were collected through information recorded in the patient diary and actively solicited by the investigator during the scheduled visits and coded in accordance with Medical Dictionary for Regulatory Activities (MeDRA).

6.1.12.2 Overview of Adverse Events

All 27 subjects that were enrolled and treated on the study constituted the safety analysis population. Overall, both doses were well tolerated.

During the study, 12 subjects (44%) experienced a total of 25 treatment emergent adverse events (TEAE). Eight patients experienced 15 TEAEs in the 75 mcg/kg dose arm, with a total mean number of study drug administrations of 50 per patient and 6 patients experienced 10 TEAEs in in 225mcg/kg arm with total mean number of administration of 22.5 per patient.

Table 16: Adverse Events

Adverse Event By Organ System	Severity	75 mcg/kg N=25	225 mcg/kg N=25	Overall population N=27
Infections and Infestations				
Influenza	Moderate		1	1
Nasopharyngitis	Moderate	1	2	3
Acute tonsillitis	Severe	1		1
Sinusitis	Moderate		1	1
Gum infection	Moderate	1		1
Nervous System Disorder				
Headache	Moderate	1	1	2
Headache	Mild	2		2
Subarachnoid hemorrhage	Moderate	1		1
Respiratory, Thoracic and Mediastinal disorder				
Allergic Rhinitis	Moderate	1		1
Sore Throat	Mild		1	1
Dyspnea	Mild		1	1
Musculoskeletal and connective tissue disorder				
Ankle pain	Moderate	1		1
General disorders and administration site conditions				
Infusion site discomfort	Mild	4		4
Infusion site hematoma	Mild	2		2
Investigations				
AST/ALT elevation	Mild		2 1	2 1
Fever	Moderate		1	

Treatment Emergent Adverse Events
Four episodes of headache occurred in 3 subjects (14%) which were not considered by the FDA reviewer to be related to SEVENFACT. Nasopharyngitis occurred in 3 subjects (11%) also not considered by the FDA reviewer as related to study drug administration. Please refer to Appendix A for further details.

Two SAEs occurred in one subject and were not related to study drug administration as determined by the FDA reviewer. These were acute tonsillitis and subarachnoid hemorrhage. They are described in detail under section 6.1.12.4.

The following adverse events were determined by the FDA reviewer to be related to the study drug.

-Febrile illness occurred in a 12-year-old subject who was in the 225 mcg/kg group. Fever developed 4 hours after receiving dose of SEVENFACT for the treatment of a bleed. Fever lasted for 2 days and was managed symptomatically and resolved. It was rated as moderate by the investigator. He was treated with SEVENFACT for 15 bleeding events without any adverse events prior to this febrile episode.

-4 episodes of infusion site discomfort and 2 episodes of infusion site hematoma all occurred in 1 patient during 4 bleeding episodes and occurred on the day study drug was administered. These were rated as mild and all resolved.

There were no significant differences in the type and frequency of adverse events between the two arms. A dose-safety relationship wasn't observed.

Among the 5 subjects that were < 18 years if age, 3 subjects (60%) developed 6 treatment emergent adverse events include fever, nasopharyngitis, headache, arthralgia. There does not appear to increased risk of adverse events in the adolescent subpopulation.

Reviewer's Comment-
Fever, infusion site discomfort and infusion site hematoma will be included in the label as a treatment emergent adverse reactions.

6.1.12.3 eaths

No deaths were reported in this study.

6.1.12.4 nfatal Serious Adverse Events

SAE narrative
Two SAEs were reported in a single subject b) (6) in this trial. The SAEs occurred in a 19 year old subject who developed acute tonsillitis requiring hospitalization 5 days after receiving a dose of 75 mcg/kg dose of SEVENFACT. Seven days following the last dose of SEVENFACT, the subject developed clinical symptoms of a cerebrovascular event, with MRI confirming a left sided 6-8 mm subarachnoid hemorrhage and subsequent acute subdural hematoma of the left brain hemisphere. He was treated with FEIBA, NOVOSEVEN and anti-fibrinolytics with resolution of the bleed and related symptoms. Since the event is a bleeding event, it is unlikely to be related to SEVENFACT based on the mechanism of action of recombinant FVIIa and likely related to the underlying disease. The subject was discharged from the hospital, completed the study but did not receive any additional study drug.

6.1.12.5 Adverse Events of Special Interest (AESI)

No episodes of thromboembolic events, development of neutralizing antibodies or hypersensitivity reactions were reported in this trial.

Reviewer's comments: Thrombogenicity, immunogenicity and hypersensitivity were not observed in the study. However, these events are known adverse events related to the product class. The reviewer recommends including these events in the Warnings and Precautions Section in the label.

6.1.12.6 inical Laboratory Test Results

Adverse Events – Laboratory monitoring
-Immunogenicity: Two subjects had positive screening antibodies for Factor VIIa; however, the confirmatory tests for antibody were negative at screening and at follow up (of up to 24 weeks) except for one subject during one visit (week 12). None of these subjects developed neutralizing antibodies post exposure.

Abnormal Liver Function Tests: One subject with a history of hepatitis C who had baseline elevation of AST/ALT developed transient worsening of transaminitis (peak- grade 3) during the study. There was no association between exposure to SEVENFACT and worsening of Liver Function Tests (LFTS). His LFTs improved to baseline by the end of the study.

6.1.12.7 Dropouts and/or Discontinuations

No subjects discontinued from the study due to adverse events. Although five subjects dropped out of the study, they were included in the safety analysis population. Thus, the discontinuations did not impact the robustness of the safety assessments.

6.1.13 STUDY SUMMARY AND CONCLUSIONS

The primary efficacy endpoint of the study was the proportion successfully treated mild or moderate bleeding episodes at 12 hours after initial study drug administration. Primary efficacy analysis compated the proportion of successfully treated bleeding events in both 75mcg/kg and 225mcg/kg doses to a pre-specified objective performance criterion (OPC) of 55%. Primary efficacy analysis showed that both doses 75 mcg/kg and 225 mcg/kg doses were successful in treating mild or moderal bleeding events. The proportion of successfully treated mild/moderate bleeding episodes was 81.7% (95% CI: 72.3-91.2) for the 75 mcg/kg dose arm and 90.8%(95% CI: 83.7- 98) for the 225mcg/kg arm. Statistical testing of the alternative hypothesis comparing the proportion of successfully treated bleeding events with OPC of 55% was significant ($p<.001$) at 1 sided .0125 significance level for both regimens.

Overall, both doses were well tolerated. There were no deaths, thromboembolic events or neutralizing inhibitors reported in this clinical study. Adverse events

that were associated with the administration of SEVENFACT included one episode of fever, four episodes of infusion site discomfort and two episodes of infusion site hematoma. Two SAEs of acute tonsillitis and subarachnoid hemorrhage occurred in1 subject that were not related to SEVENFACT. No study discontinuations occurred due to adverse.

The conclusions from the primary efficacy analysis are based on the re-adjudicated outcomes. This study met the success criteria for the primary efficacy analysis with and without the re-adjudicated outcomes. Both doses 75 mcg/kg and 225 mcg/kg achieved statistically significant results as compared to the pre-specified objective performance criteria. The study was not powered to compare the efficacy of the two dose regimens however the proportion of successfully treated mild/moderate bleeding episodes for the 225 mcg/kg regimen was higher than that for 75 mcg/kg regimen. The rate of treatment failure at 12 hours was higher for the 75 mcg/kg dosing (18%) than for 225 mcg/kg dose (9%). The clinical reviewer recommends that the label include information for the efficacy outcomes for both doses in Section 14 of the label. The recommendation to include the higher dose (225 mcg/kg) in the label is based on the shorter time to hemostatic response noted in this arm, the efficacy data noted in a limited number of subjects with severe bleeding and the favorable safety data. The limitation of the efficacy conclusion relate to the small sample size (n=3) for the treatment of severe bleeding events. The limitations of the safety data relate to exclusion of subjects who are at risk for thrombosis.

6.2 Trial #2

TRIAL # 2 :GTC-FVIIA-005-11

A Phase 1b, dose escalation study to assess the safety, pharmacokinetics and pharmacodynamics of coagulation Factor VIIa (Recombinant) in Congenital Hemophilia A or B patients.

Study Duration- October 9, 2012 through June 4, 2013.

Primary Objective
-To assess the Pharmacokinetic (PK) and Pharmacodynamic (PD) properties of doses of Coagulation Factor VIIa (Recombinant) in male congenital Hemophilia A or B patients.

Secondary Objective
-To assess the safety of 3 doses of Coagulation Factor VIIa (Recombinant) in male congenital Hemophilia A or B patients.

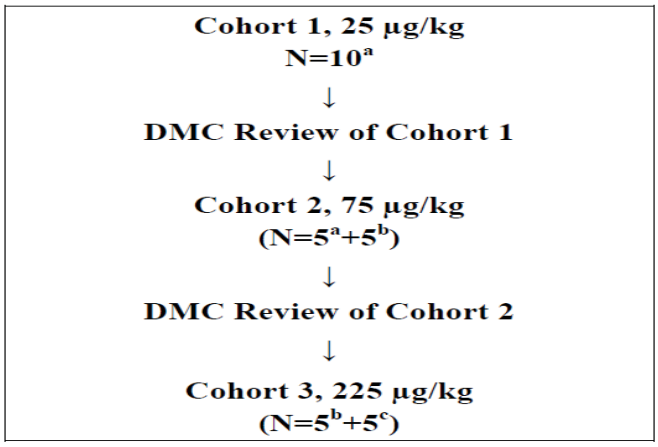
6 2 2 **DESIGN OVERVIEW**

Design Overview

This is a single arm, open label, dose escalation trial that enrolled subjects to 3 dose cohorts of 25 mcg/kg, 75 mcg/kg and 225 mcg/kg. The study permitted subjects to be exposed to two doses in an escalating manner (for example, subjects who received 75 mcg/kg received 225 mcg/kg dose subsequently).

Each dose cohort required that at least 10 subjects were treated with the assigned dose.
The schema below depicts the number of subjects who were treated and the dose they received.

Figure 2: Dosing Schema



a) Newly enrolled patients
b) Patients previously treated in Cohort 1
c) Patients previously treated in Cohort 2

Source: BLA 125641/0 ;Clinical Study Report:GTC-FVIIa-005-11,Page 24.

6.2.3 POPULATION

.
Inclusion Criteria-
1. Males with a diagnosis of moderate or severe congenital Hemophilia A and/or B (with or without inhibitors)
2. At least 18 years or older, up to and including 75 years of age

Key Exclusion Criteria-
1. Body weight >105 kg (231 lbs.)
2. Immunosuppression; CD4 count<200/mcl, no systemic immunosuppression <30 days prior to enrollment.
3. Allergy or hypersensitivity to rabbits
4. Platelet count <100,000/mL
5. Active, ongoing bleeding for which the patient was being treated, or treatment for a bleeding was stopped within 24 hours of the time of study drug administration
6. Significant liver disease (hepatic enzymes >3 times the upper limit of normal) and/or renal impairment (creatinine >2 times the upper limit of normal)

7. History of arterial and/or venous thromboembolic events within 2 years prior to first dose of study drug, arterial stent in place or clinically significant atherosclerotic disease (e.g., angina pectoris, peripheral vascular disease)
8. Patient must not have received any FVIIa product for at least 72 hours prior to administration of rhFVIIa.

Reviewer's Comments- This study enrolled relatively healthy subjects with or without Factor VIII or IX inhibitors in the non-bleeding state. This study population differed from trial #1 where the enrollment criteria required subjects with moderate/severe hemophilia with inhibitors requiring bypassing agents and frequent bleeding episodes to be enrolled. Due to the differences in the patient population, the integrated analysis of efficacy will not be included in the clinical review.

6.2.4 STUDY TREATMENTS OR AGENTS MANDATED BY THE PROTOCOL

One lot of SEVENFACT (A1C03) SEVENFACT was used in this trial. To obtain a final concentration of 1mg/ml, 5 mg vials of lyophilized powder were reconstituted with water for injection.
Subjects recieved two administrations of rhFVIIa at a dose of 25 mcg/kg,75 mcg/kg or 225 mcg/kg in one of three sequences (25/75, 25/225, 75/225).

6.2.5 DIRECTIONS FOR USE

Please refer to 6.1 for details.

6 2 6 SITES AND CENTERS

The study was conducted at 3 sites in 2 countries:

- Leiden, Netherlands - 7 subjects
- IL,USA – 4 subjects
- Sacramento, CA -4 subjects

6.2.7 SURVEILLANCE/MONITORING

Physical examination was performed at screening and at day 28+/-2 day follow up visit.

Table 17: Schedule of Events

Evaluation	Screening Days -21 to -1	Treatment Period (First and Second)														Follow-up (Day 28± 2)
		Base-line[1]	Min -30	Pre-dose (0 hr)	Study drug	Min 5	Min 15	Min 30	Hr 1 & 2	Hr 4	Hr 6	Hr 8	Hr 12	Hr 24-36	Day 14±1	
Informed Consent	X															
I/E Criteria	X	X														
Demographics	X															
Medical History	X															
Physical Examination	X[2]	X[3]														X[2]
Safety Lab Tests	X[4]	X[5]												X	X	
Vital Signs[6, 7]	X	X				X	X	X	X		X		X	X		
ECG[7]	X													X		
Study Drug Administration					X											
PK Blood Sample			X	X		X	X	X	X	X	X	X	X	X		
PD Sample Set 1[8]			X	X		X	X	X	X	X	X	X	X	X		
PD Sample Set 2[9]			X			X		X	X		X		X	X		
PF4			X			X					X			X		
AE Assessment	Throughout Study															
Conmed Assessment	X	X												X		X
Immunogenicity[10]		X												X	X	X
Storage sample		X														X

[5] Except when screening was done within 48 hours prior to first administration of study drug and no clinically significant events, e.g., bleedings, have occurred in the meantime.

[6] Include blood pressure, pulse, respiratory rate, and temperature.

[7] Patients will have a 2-minute rest in a supine position before vital signs are assessed or ECG performed

[8] PD set 1: TGT, aPTT, PT

[9] PD set 2: F1+2, D-dimer, TAT, ROTEM

[10] Serum sample. Also includes storage serum sample for potential future use (e.g. infectious disease of immunological evaluations)

Source: Adapted from GTC-FVIIa-005-11, Table 1b.

6.2.8 ENDPOINTS AND CRITERIA FOR STUDY SUCCESS

.There were no formal efficacy endpoints outlined in this protocol. PK variables assessed in this study include terminal half-life,AUC, mean residence time ,clearance,volume of distribution at steady state, maximum concentration achieved (Cmax) and time at which maximum concentration is achieved(Tmax). Pharmcodynamic variables assessed included thrombin generation test with and without platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT),rotational thromboelastometry including maximal clot firmness,prothrombin fragments 1+2, d-dimer and thrombin-anti-thrombin complex. Safety assessment was perfomed on all subjects enrolled and treated on this study.

6.2.9 Statistical Considerations & Statistical Analysis Plan

No comparative statistical tests were planned between dosages. All analyses were exploratory and descriptive analysis are used for PK/PD analysis.

6.2.10 STUDY POPULATION AND DISPOSITION

All subjects who were enrolled were treated and included in the efficacy and safety analysis.

6.2.10.1 Population enrolled/analyzed-

Eighteen subjects were screened, 15 enrolled and treated and considered evaluable for pharmacokinetic and safety assessment.

6.2.10.1.1 Demographics

All subjects in this study were male as mandated by the protocol. Ages ranged from 20-61 years. The mean age of the study population was 33 years. Body weight of the subjects ranged from 60.5 to 102.7kg. Sixty two percent of subjects were white, 15% were Hispanics, 13% were Asians and 6% were African American.

6.2.10.1.2 edical/behavioral characterization of the enrolled population

A total of 73.3% of subjects had a diagnosis of hemophilia A and 26.7% had a diagnosis of hemophilia B. A total of 80% of subjects had severe hemophilia and 20% had moderate hemophilia. A total of 27% of subjects had detectable low-titer inhibitors to FVIII or FIX at screening and 40% had hemophilic arthropathy.

Reviewer's comments- This study enrolled hemophilia subjects with or without inhibitors as pharmacokinetics or pharmacodynamic effect of Factor VIIa is not affected by the presence of inhibitors to Factor VIII or IX.

6.2.10.1.3 Subject Disposition

Table 18 summarizes subject disposition. All subjects completed the study and none withdrew; however, one subject was lost to follow up.

Table 18: Subject Disposition

Disposition	rhFVIIa 25 µg/kg n (%)[1]	rhFVIIa 75 µg/kg n (%)[1]	rhFVIIa 225 µg/kg n (%)[1]	Total n (%)
Screened				18 (100.0%)
Treated	10 (100.0%)	10 (100.0%)	10 (100.0%)	15 (83.3%)
Completed per cohort up to 24-36 hr	10 (100.0%)	10 (100.0%)	10 (100.0%)	15 (83.3%)
Completed study				14 (77.8%)
Reasons for withdrawal				
- Lost to follow-up	-	-	-	1

[1] Period covering period until 24-36 hours post-administration

.Source: Adapted from CSR GTC-FVIIa-005-11, Table 2.

Protocol Deviations
Multiple minor deviations occurred during the course of the study, none of which impacted PK, PD, or safety outcomes.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Efficacy was not specifically evaluated in this study. The primary endpoints pertained to evaluation of PK/PD as well as safety.

Pharmacokinetic (PK) analyses

Please refer to the Clinical Pharmacology review memo.
The conclusions of the analyses were that there was a dose dependent relationship to maximum concentration and AUC. The half-life of SEVENFACT was approximately 2 hours for all dose groups.

Pharmacodynamic (PD) analyses

PD markers assessed with TGT (thrombin generation test) with platelets, aPTT and MCF(maximal clot firmness). Dosing with 75 mcg/kg every 2-3 hours provided a PD effect that was adequate for hemostasis. Dosing with 225 mcg/kg allowed for longer interval before the need for repeat dosing.

6.2.11.2 Analyses of Secondary Endpoints

.
Not applicable.

6.2.11.3 Subpopulation Analyses

This Phase 1 trial enrolled adult males with severe hemophilia A or B with or without inhibitors and in an overall general healthy state. The overall homogeneity of the enrolled population and the small sample size, limit the validity of subpopulation analyses.

6.2.11.4 Dropouts and/or Discontinuations

One subject dropped out of the study and was lost to follow up. He received both the treatment doses and completed 6 study evaluations up to 24-36 hours after receiving second administration of study drug. He was included in safety analysis.

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable

6.2.12 **SAFETY ANALYSES**

6.2.12.1 Methods

All 15 subjects that were treated in the study received 2 escalating doses of rhFVIIa and were included in the safety analysis.

Safety assessments in this trial included physical examination, ECG, vital signs, clinical laboratory testing, immunogenicity testing, assessment of coagulation-activation markers and monitoring of adverse events. Adverse event data were collected during monitoring of subjects after infusion of the drug product and during scheduled visits.

Adverse events of special interest included allergic reactions to the drug product and thromboembolism after exposure to the product.
Prothrombin fragments 1 and 2, d-dimer and thrombin-antithrombin complex are markers of coagulation activation and can indicate potential of over-coagulation and risk of thrombosis.

Immunogenicity testing for anti-FVIIa antibodies was done prior to study drug administration, at 24-36 hours and at the 14 day visit after initial and second administration of study drug. This was repeated at the 28 day follow up visit.

Safety assessment was done at 24 to 36 hours,14+/-1 day after each study drug and 28+/-2 days after last administration.
Vital signs were assessed at baseline and 5, 15, 30, 60, 120 minutes, 6 hour,12 hours, and 24 hours after the first and second infusion of study drug to assess for any acute infusion or allergic reactions.

6.2.12.2 Overview of Adverse Events

A total of 39 treatment emergent adverse events (TEAE) occurred in 11 subjects during the study as depicted in Table 19 below.

Table 19: Adverse Events

Adverse Event By Organ System	Severity	25mcg/kg (n=10)	75mcg/kg (n=10)	225mcg/kg (n=10)	Overall Population (n=15)*
Nervous system disorder					
Headache	Mild	1	2	1	4
	Moderate			1	1
Dizziness	Mild	1	2		3
Metallic taste during infusion	Mild		1		1
General Disorders and administration site conditions					
Fatigue	Mild	2			2
Influenza like symptoms	Mild	1			1
Chills	Mild		1		1
Constriction in chest	Mild		1		1

Adverse Event By Organ System	Severity	25mcg/kg (n=10)	75mcg/kg (n=10)	225mcg/kg (n=10)	Overall Population (n=15)*
Musculoskeletal and connective tissue disorder					
Hemarthrosis	Mild	9		1	10
Muscle hemorrhage	Mild	1	1	1	3
Myalgia	Mild			1	1
Vascular Disorder					
Left cheek bleed	Mild			1	1
Gastrointestinal disorder					
Nausea	Mild	1			1
Gingival Bleeding	Mild			1	1
Ear and Labyrinth Disorders					
Rt. ear pain	Mild	1			1
Rt. ear drainage	Mild	1			1
Auricular swelling	Mild	1			1
Bruising of rt. ear	Mild	1			1
Blood and Lymphatic system disorder					
Lymphadenopathy	Mild			1	1
Investigations^	Mild	1			1
Skin and subcutaneous disorders					
Flushing	Mild		1		1
Cardiac Disorders					
Tachycardia	Mild		1		1

*Each subject received two escalating doses
^Transient 2+ proteinuria on urine dipstick

Reviwer's comments
Bleeding events were included as adverse events on in this Phase1 trial. Most common treatment emergent adverse event was bleeding with 16 episodes in 7 subjects (46%). Bleeding was related to underlying hemophilia and not secondary to SEVENFACT.

Treatment emergent adverse events possibly related to administration of SEVENFACT included 2 episodes of dizziness in 1 subject (6.6%) and 5 episodes of headache in 3 subjects(20%).One episode of hypersensitivity reaction occurred after exposure to SEVENFACT that is summarized in Section 6.2.12.5 and considered related to SEVENFACT.

6.2.12.3 Deaths

No deaths were reported on the study.

6.2.12.4 Non-Fatal Serious Adverse Events

No serious adverse events were reported in the study.

6.2.12.5 Adverse Events of Special Interest (AESI)

Allergic and thromboembolic events were protocol specified AESI.
No episodes of thromboembolism occurred with administration of rhFVIIa.. A single episode of flushing, chest tightness, shakiness, metallic taste occurred in Subject b) (6) This episode was accompanied by transient tachycardia, low grade temperature and mild drop in blood pressure. Symptoms started immediately with the infusion of the first dose of 75 mcg/kg of SEVENFACT and lasted about 45 minutes. Symptoms resolved without any intervention and did not recur with rechallenge with a higher dose of 225 mcg/kg. Per the investigator, these symptoms were related to cold exposure during travel to treatment center. Based on the proximity of occurrence of symptoms with the infusion of study drug and change in vital signs occurring with acute symptoms, this episode is consistent with acute hypersensitivity reaction to study drug.

6.1.12.6 Clinical Laboratory Test Results.

Immunogenicity Testing-
The screening assay for anti-rhFVIIa antibody was positive in 3 out of 15 subjects prior to administration of study drug, 2 out 15 were positive 24 hours after first drug exposure and 5 out of 15 were positive at day 14 visit after first drug exposure. Confirmatory assay was negative in all samples. One subject (Subject (b) (6) did not adequate sample for confirmatory testing at 24 hours, however, all subsequent samples from the patient were negative. None of the subjects tested positive for anti-rabbit milk protein antibodies.

Prothrombin Fragments 1+2 are markers of excessive coagulation and showed dose dependent increases with peaks 1-2 hours post infusion as expected due to thrombin formation. The highest observed median change from baseline was noted in following dosign with the 225 mcg/kg dose. Levels returned to baseline 6-12 hours post infusion.

D-dimer levels did not show any clinically relevant changes over the course of the study.
Thrombin-antithrombin(TAT) complexes were increased in a dose dependent manner when assessed 30 minutes post infusion compared to baseline.

Reviewer's Comments-
No evidence of immunogenicity was noted with SEVENFACT in this trial as all confirmatory assays for anti-rhVIIa antibodies were negative in screen positives.

Prothrombin fragements 1+2 and TAT elevation was noted after administration of SEVENFACT; however, the elevation was for a short duration and not associated with evidence of thrombosis. The results of the immunogenicity testing and Prothrombin Fragments 1+2 in this study are consistent with the clinical findings from Study 1.

6.2.12.7 Dropouts and/or Discontinuations

There were no drop outs from the study due to adverse drug effects.

6.2.13 Study Summary and Conclusions

The PK studies confirmed a dose relationship between PK parameters (AUC and Cmax) and the PD studies confirmed a PD effect that 75mcg/kg dosing every 2-3 hours provided a PD effect that was adequate for hemostasis. The 225 mcg/kg dosing allowed for longer interval before the need for repeat dosing. Based on the results, the 75 mcg/kg and 225 mcg/kg dose were evaluated in the Phase 3 trial previously discussed.

7. INTEGRATED OVERVIEW OF EFFICACY

The differences in the population, objectives and dosing between the Phase 1 and Phase 3 studies preclude an integrated analysis of efficacy.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The Phase 1 and Phase 3 studies were not analyzed in a pooled manner due to the differences in the population and dosing. However, the safety data were analyzed for consistencies in the adverse events findings between the two studies.

8.2 Safety Database

The safety database consisted of a total of 42 subjects in the Phase 1 and Phase 3 studies.

The 120 day safety update report was received for all subjects enrolled in clinical studies with SEVENFACT. The data cutoff date was 10/1/2016. The key safety findings from other studies are presented below.

PERSEPT 2; Safety and efficacy study in subjects with hemophilia A and B with inhibitors aged 0-12 years.

-A 9-year old African American male was randomized to 225 mcg/kg dosing and received first study drug administration on (b) (6) . He developed paresis due to intracranial bleed on (b) (6) and this resolved on (b) (6) . Patient recovered with resolution of paresis. He did not complete the study. Investigator felt SAE is unrelated to study treatment.

- A 1-year old male was randomized to 75 mcg/kg arm and treated for bleeding event on (b) (6). He developed severe diarrhea on 3/9/2016 and it resolved on 3/11/2016 without sequelae. This event was considered to be unrelated to the study drug.

Reviewer's Comments-Both the adverse events outlined above for PERSEPT-2 trial are not related to the study drug. Recombinant Factor VIIa is associated with thrombosis and not bleeding. Diarrhea is also not an expected side effect of this pharmacologic category.

PERSEPT 3 trial; Safety and efficacy trial in surgical setting.

- (b) (4), (b) (6)

Reviewer's Comment
Reviewer agrees with the Applicant's assessment of the adverse events noted in the PERSEPT 3 trial. The (b) (4) to the clinical protocol to enhance patient safety.

8 2 1 STUDIES/CLINICAL TRIALS USED TO EVALUATE SAFETY

The Phase 1 (Study 2) and Phase 3 (Study 1) were used to evaluate safety.

8.2.2 OVERALL EXPOSURE, DEMOGRAPHICS OF POOLED SAFETY POPULATIONS

The study designs were distinct and did not allow for pooled evaluation as noted earlier.

8.2.3 CATEGORIZATION OF ADVERSE EVENTS

See the individual study sections.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

Not applicable

8.4 Safety Results

8.4.1 DEATHS

No deaths occurred in the study.

8.4.2 NONFATAL SERIOUS ADVERSE EVENTS

Two nonfatal SAEs, intracerebral hemorrhage and acute tonsillitis, were observed in the Phase 3 study in one subject. These events were considered as unrelated to the study drug. One mild hypersensitivity reaction was noted in the Phase 1 study and was considered to be related to the study drug treatment.

8.4.3 STUDY DROPOUTS/DISCONTINUATIONS

Please refer to Studies 1 and 2.

8.4.4 COMMON ADVERSE EVENTS

The most common adverse event was hemarthrosis expected event related to efficacy. Headaches and dizziness were also noted as common adverse events.

8.4.5 CLINICAL TEST RESULTS

There were no neutralizing antibodies to FVII

8.4.6 SYSTEMIC ADVERSE EVENTS

Please refer to Non-fatal serious adverse events.

8.4.7 LOCAL REACTOGENICITY

episodes of infusion site discomfort and 2 episodes of infusion site hematomas were noted in 1 subject.

8.4.8 ADVERSE EVENTS OF SPECIAL INTEREST

No thromboembolic events occurred. One subject developed a mild hypersensitivity reaction.

8.5 Additional Safety Evaluations

8.5.1 DOSE DEPENDENCY FOR ADVERSE EVENTS

Not applicable

8.5.2 Time Dependency for Adverse Events

Not applicable

8.5.3 Product-Demographic Interactions

Not applicable

8.5.4 Product-Disease Interactions

Not applicable

8.5.5 Product-Product Interactions

Not applicable

8.5.6 Human Carcinogenicity

Not applicable

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.5.8 Immunogenicity (Safety)

None of the subjects developed a neutralizing antibody to FVII.

8.5.9 Person-to-Person Transmission, Shedding
Not applicable

8.6 Safety Conclusions

No substantial safety issues were identified.

9. Additional Clinical Issues

9.1 Special Populations

Not applicable

9.1.1 Human Reproduction and Pregnancy Data

All subjects were male, thus safety of treatment during pregnancy was not evaluated. Reproduction data was not included in the study report.

9.1.2 Use During Lactation

All subjects were male, thus safety of treatment during lactation was not evaluated.

9.1.3 Pediatric Use and PREA Considerations

Five adolescent subjects (≥12 years) were enrolled in the Phase 3 study. There were no pediatric subjects in the Phase 1 study. The efficacy in the adult and

adolescent populations was similar. There were no safety concerns in the adolescent age group

A study is ongoing in subjects <12 years of age. The Application was presented to the Pediatric Review Committee (PeRC), the deferral request was discussed and the PeRC recommended that a pediatric deferral for patients < 12 years could be granted if a marketing approval is planned.

9.1.4 IMMUNOCOMPROMISED PATIENTS

The study did not enroll immunocompromised patients.

9.1.5 GERIATRIC USE

None of the subjects were 65 years or older. A total of 3/27 subjects were between the ages of 50 and 60 years of age in the Phase 3 study and one subject was 61 years of age in the Phase 1 study. No differences in efficacy were noted in three subjects in the Phase 3 studies as compared to the remainder of the subjects.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

Not applicable.

10. CONCLUSIONS

Integrated analysis of efficacy was not performed as there were no efficacy assesments in the Phase 1 study. The safety evaluations from the two studies did not reveal any major safety concern

Decision Factor	Evidence and Uncertainities	Conclusions and Reasons
Analysis of Condition	• The development of inhibitors to Factor VIII or Factor IX is the most significant complication of hemophilia treatment • 33% of subjects with severe hemophilia A and 3% in severe Hemophilia B develop inhibitors. • Patients with low responding inhibitors (<5BU) continue treatment with factor replacement at same or higher dose. • Once inhibitor titer is >5BU, then factor replacement is ineffective and bypassing agents are needed.	• Bleeding complications from neutralizing (inhibitors) to FVIII and FIX is a serious and life-threatening event. • Chronic bleeding is associated with joint damage, is progressive and debilitating and adversely affects the quality of life. • The study included subjects with high and low titer inhibitors.
Unmet Medical Need	• Activated prothrombin complex concentrate and recombinant factor VIIa are approved as bypassing agents to treat bleeding episodes in subjects with hemophilia A and B with inhibitors. • Recombinant factor VII product are administered every 2-3 hours until hemostasis is achieved.	• There is no unmet need in terms of the need for bypassing agents. Nevertheless, availability of additional recombinant products for use in the US population is considered a benefit.
	• The Applicant conducted a Phase 3 single arm study in subjects with mild/moderate bleeding from inhibitors to factor VIII and IX. The study met its primary efficacy analysis criteria for success. The criteria for success was based on an objective performance threshold derived from historical data. Therefore, the study was an adequate and well controlled study.	• The evidence for clinical benefit for hemostatic response was primarily based on assessments in patients with mild/moderate bleeding. Three subjects were treated with the higher dose (225 mcg/kg). Thus, there is limited efficacy data in subjects with severe bleeding. • Five adolescent subjects were included in the study and represent a reasonable sample size for this population. The efficacy findings in this age group is consistent with the findings in 22 adult subjects.

Risk	• No substantial risks related to SEVENFACT were noted. For the class of products, the risks of thrombogenicity and allergic reactions are adverse events of special interest (AESI). No AESI were observed.	• The study excluded subjects at high risk for thromboembolic events. Thus, there is limited external validity of the safety results in this risk group.
		• Overall the benefits of the product outweigh the theoretical and observed adverse risks.

11.2 Risk-Benefit Summary and Assessment

Potential Benefit
The study met the success criteria for hemostatic efficacy. The data demonstrates that SEVENFACT is effective in the control and prevention of bleeding. The data to demonstrate control of severe bleeding was limited. As the PK and PD data support a dose dependent relationship, it is reasonable to consider the higher dose (225 mcg/kg) in the dosage section of the label.

Potential Risks
The risks from treatment are minimal.

11.3 Discussion of Regulatory Options

Indication: On demand treatment and control of bleeding episodes occurring in adolescent and adult patients with hemophilia A or B with inhibitors.

Dose: 75 mcg/kg every three hours or 225 mcg/kg followed by a 75 mcg/kg 9 hours following the first infusion and repeated every 3 hours until hemostasis is achieved.

11.4 Recommendations on Regulatory Actions

The clinical reviewer recommends approval of SEVENFACT for the on-demand treatment and control of bleeding in adults and adolescent patients with congenital hemophila with inhibitors.

11.5 Labeling Review and Recommendations

A Complete response related to manufacturing issues is anticipated. Therefore, there are no recommendations for labelling considerations at this time.

11.6 Recommendations on Postmarketing Actions

No safety signals were observed. Therefore, the review team does not recommend a post-marketing related study for safety. The deferred pediatric study would be a post-marketing required study if SEVENFACT were to be licensed.

APPENDIX A: TYPE OF BLEEDING

Bleed	Description	Examples
Mild	A bleed that just started and had little symptoms, i.e., little or no pain, little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity	• Early onset muscle and joint bleeds with no visible symptoms such as little or no change in the range of motion of affected joint (if joint bleed); mild restriction of mobility and activity • Scrapes, superficial cuts, bruises, superficial mouth bleeds and most nose bleeds
Moderate	A bleed that involved swelling or pain including some decrease in range of motion of affected joint (if joint bleed) or moderate decrease in mobility and activity	• Advanced soft tissue and muscle bleeds into the limbs • Bleeding into the joint space, such as the elbow, knee, ankle, wrist, shoulder, hip, foot or finger
Severe	Severe bleeds that were potentially life/limb threatening, produce significant blood loss, pain or can cause permanent nerve damage	• Mouth and neck region – Bleeding from the floor of the mouth, pharynx, or epiglottic area can result in partial or complete airway obstruction. • Complicated joint bleeds – Hip joint or acetabular haemorrhages • Iliopsoas haemorrhages • Bleedings that led to compartment syndrome such as in hand, wrists, forearm and anterior or posterior tibial compartments • Central nervous system haemorrhages • Gastrointestinal – bleeding that occurred in stomach or intestines • Acute haemorrhage - such as bleeding into the abdomen • Bleeding from major trauma

Source: CSR PERSEPT-1 Table 1

APPENDIX B : RE-ADJUDICATED BLEEDING EVENTS

Table 20: Soft tissue bleeding events re-adjudicated by the FDA clinical reviewer

Insert text here

Subject ID	Bleed ID	Location	Dose mcg/kg	Applicant's Designation	Reviewer's Designation	VAS Baseline	VAS 12 hours
(b) (6)	(b) (6)	Rt. Elbow*	75	Success	Failure	44	45
(b) (6)	(b) (6)	Rt. Hip*	75	Success	Failure	45	50
(b) (6)	(b) (6)	Rt. Elbow*	225	Success	Failure	30	50
(b) (6)	(b) (6)	Rt. Knee*	225	Success	Failure	30	50
(b) (6)	(b) (6)	Lt. elbow*	75	Success	Failure	4	4

Source: FDA reviewer

Table 21: Re-adjudicated bleeding events with pain confounded by concomitant pain medications

Subject ID	**Bleed ID**	**Dose given**	**Medication**
(b) (6)	(b) (6) at 16:00. Left Ankle	75 mcg/kg	Dexketoprofen
(b) (6)	(b) (6) at 9:30 am Left shoulder	225 mcg/kg	Ibuprofen
(b) (6)	(b) (6) at 11:40 am left hip	75 mcg/kg	Acetaminophen
(b) (6)	(b) (6) at 7:20 am left knee	75 mcg/kg	Acetaminophen
(b) (6)	(b) (6) at 14:00 Rt. wrist and hand	75 mcg/kg	Acetaminophen

Source: FDA reviewer

APPENDIX C: ADVERSE EVENTS

Table 22: Treatment Emergent Adverse Events For RB-FVIIa-006-13

Subject ID	Dose	Adverse Event	Relationship with SEVENFACT
(b) (6)	225mcg/kg	Influenza	No
(b) (6)	75mcg/kg	Nasopharyngitis	No
(b) (6)	75mcg/kg	Acute tonsillitis	No
	75mcg/kg	Subacute hemorrhage	No
(b) (6)	75mcg/kg	Allergic rhinitis	No
(b) (6)	225mcg/kg	Nasopharyngitis	No
(b) (6)	75mcg/kg	Ankle pain	No
(b) (6)	75mcg/kg	Headache	No
(b) (6)	225mcg/kg	Nasopharyngitis	No
	225mcg/kg	Sinusitis	No
	225mcg/kg	Fever	Yes
(b) (6)	75mcg/kg	Gum infection	No
(b) (6)	75mcg/kg	Infusion site discomfort	Yes
	75mcg/kg	Infusion site discomfort	Yes
	75mcg/kg	Infusion site discomfort	Yes
	75mcg/kg	Infusion site discomfort	Yes
	75mcg/kg	Infusion site hematoma	Yes
	75mcg/kg	Infusion site hematoma	Yes
(b) (6)	225mcg/kg	Dyspnea	No
(b) (6)	225mcg/kg	Headache	No
(b) (6)	225mcg/kg	Sore throat	No
(b) (6)	225mcg/kg	AST/ALT elevation	No
	225mcg/kg	AST/ALT elevation	No
	75mcg/kg	Headache	No
	75mcg/kg	Headache	No

Source: FDA reviewer

*****Do Not Change Anything Below This Line*****