Clinical Pharmacology BLA Review

Division of Clinical Evaluation and Pharmacology/Toxicology

Office of Tissues and Advanced Therapy

BLA	125641/0
Product	Coagulation Factor VIIa (Recombinant); rhFVIIa, LR769
Sponsor	Laboratorie Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.)
Indication	For on-demand treatment and control of bleeding in adolescent and adult hemophilia A or B patients with inhibitors to FVIII or FIX.
Date Received	October 13, 2016
Reviewer	Xiaofei Wang, Ph.D. Clinical Pharmacology Reviewer, General Medicine Branch 2 Division of Clinical Evaluation and Pharmacology/Toxicology
RPM	Mark Levi
Through	Tejashri Purohit-Sheth, M.D., FACAAI, CQIA Director Division of Clinical Evaluation and Pharmacology/Toxicology

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1 EXECUTIVE SUMMARY

On October 13, 2016, Laboratorie Francais du Fractionnement et des Biotechnologies S.A. (LFB S.A.) submitted a BLA seeking approval for its Coagulation Factor VIIa (Recombinant) [rhFVIIa, LR769]. LR769 (Coagulation Factor VIIa (Recombinant), also known as rhFVIIa) is a recombinant human coagulation Factor VIIa of the vitamin K-dependent family of coagulation factors. LR769 is proposed for on-demand treatment and control of bleeding in adolescent and adult hemophilia A or B patients with inhibitors to FVIII or FIX. The proposed dose regimen is 75 µg/kg repeated every 3 hours until hemostasis is achieved, or 225 µg/kg, if hemostasis is not achieved within 9 hours, with administration of additional 75 µg/kg doses every 3 hours as needed to achieve hemostasis.

To support the approval of this BLA application, the applicant conducted two clinical studies to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of LR769. The two clinical studies involved a total of 42 patients with Hemophilia A or B with or without inhibitors. The PK and PD properties of three doses of LR769 (25 µg/kg, 75 µg/kg and 225 µg/kg) manufactured from small scale (Process A) were evaluated in Study # GTC-FVIIa-005-11. Study # RB-FVIIa-006-13 provided bridging PK information between LR769 manufactured using a small scale manufacturing process (Process A) and large scale process (Process B, to-be-marketed batch scale).

LR769 manufactured from small scale (Process A) showed linear PK at a dose range of 25 – 225 µg/kg. Comparison of PK profiles between Process A & Process B LR769 indicated that Process A & B LR769 PK profiles were similar at the dose of 75 µg/kg. At the dose of 225 µg/kg, Process B LR769 had about 75% higher peak levels (Cmax) and 40% higher area under the plasma concentration versus time curve (AUC_{0-t}) than Process A LR769. Based on submitted clinical safety data, no safety signal from Process B 225 µg/kg arm was noted.

2 INTRODUCTION/BACKGROUND

LR769 is produced in and purified from the milk of transgenic rabbits that were selected to produce this complex human glycoprotein. LR769 drug product is formulated as sterile, lyophilized dosage form (white to off-white powder) that is to be reconstituted with sterile water for injection (WFI) prior to administration by the intravenous (IV) route.

The clinical pharmacology of LR769 was assessed in two clinical studies.

- **Study # 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. The investigational drug product, LR769 used in this

study was manufactured via Process A. Pharmacokinetic assessment was conducted for three doses: 25 µg/kg, 75 µg/kg and 225 µg/kg.

- **Study # RB-FVIIa-006-13:** A Phase 3 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. During the study, LR769 was manufactured using Process B. The PK profiles of Process A and Process B LR769 were compared.

3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY FINDINGS

1) For LR769 manufactured via Process A, linear pharmacokinetics were observed after single dose administration in subjects with congenital hemophilia A or B from 25 µg/kg to 225 µg/kg.

2) Comparison of pharmacokinetics profiles between Process A & B LR769 showed that:
   - The PK profiles between Process A and Process B LR769 were similar at the dose of 75 µg/kg.
   - For the dose of 225 µg/kg, the Cmax and AUC0-t for Process B LR769 were about 75% and 40% higher than the Cmax and AUC0-t of Process A LR769, respectively. Based on submitted clinical safety data, no safety signal from Process B 225 µg/kg arm was noted.

4 LABELING COMMENTS

Reviewer's Comments:

At this moment, a complete response (CR) action is recommended by drug product reviewers, therefore, the final labeling review is not conducted. Following represents preliminary labeling recommendations.

Per drug product reviewer's comments, the tests used in PD measurements were not sensitive enough for quantitative assessment, therefore, the pharmacodynamics related labeling information is recommended to be removed from labeling.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

SEVENFACT is human coagulation Factor VIIa (Recombinant). Optimal clinical efficacy of SEVENFACT is thought to depend on the presence of functional platelets of sufficient quantity to support the action of Factor VIIa on the surface of activated platelets accumulated at the site of bleeding. Pharmacologic plasma concentrations of Factor VIIa support thrombin generation by binding to the surface of platelets and by binding to tissue factor present at the site of vascular disruption. SEVENFACT when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby achieving clot formation at the site of hemorrhage (hemostasis).

12.2 ~~Pharmacodynamics~~

~~Laboratory assessment of coagulation does not necessarily correlate with or predict the hemostatic effectiveness of SEVENFACT.~~

~~The effects of SEVENFACT on the coagulation system have been characterized using in vivo, in vitro, ex vivo and in clinical studies. The functionality of SEVENFACT as studied by the methods described demonstrated concentration related effects on:~~

- ~~Thrombin generation time assays (TGT)~~
- ~~Shortening of activated prothrombin time (aPTT)~~
- ~~Shortening of prothrombin time (PT)~~
- ~~Rotational thromboelastometry (RoTEM)~~

~~Pharmacologic plasma concentrations of Factor VIIa support thrombin generation by binding to the surface of platelets and by binding to tissue factor present at the site of vascular disruption. SEVENFACT when complexed with tissue factor can activate coagulation Factor X to Factor Xa as well as cogulation Factor IX to Factor IXa. Factor Xa in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby achieving clot formation at the site of hemorrhage (hemostasis).~~

~~In vitro assays confirmed that SEVENFACT generates factor Xa and IXa as reflected in standard coagulation tests and is capable of binding nanomolar concentrations of tissue factor. SEVENFACT activity can be neutralized by antithrombin (AT) in normal plasma concentrations.~~

~~In ex vivo experiments of hemophilia A and B patient plasma at 0.5, 1, 2, 3, 4, 6 and 10 µg/mL, SEVENFACT demonstrates increased dose dependent thrombin peaks (TGT parameters) and decreased coagulation time (PT and aPTT).~~

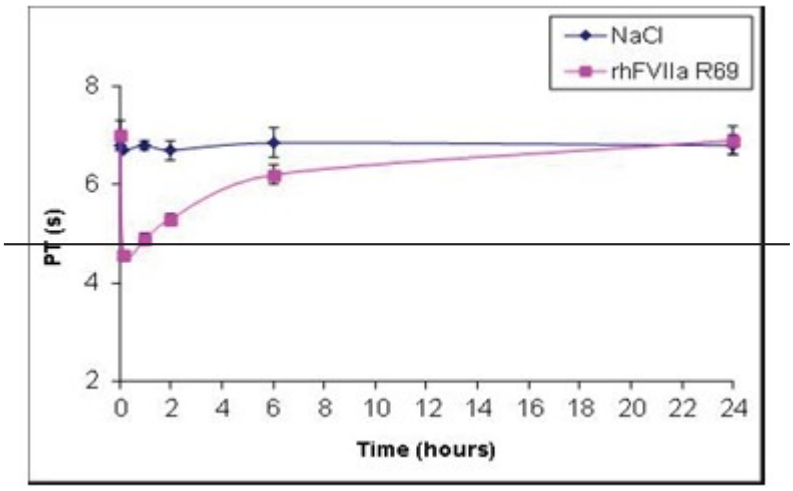
12.3~~In Vivo Pharmacodynamics~~

~~Animal Models~~

~~The in vivo pharmacological activity of SEVENFACT was evaluated in: the hemophilia A mouse (tail bleeding model), the hemophilia A dog and the rat (Wessler's venous stasis model). In a mouse bleeding model, SEVENFACT pharmacological activity was assessed at multiple doses (1, 2, 3, 4 and 6 mg/kg) by evaluating blood loss and time to hemostasis. The SEVENFACT dose dependently decreased the blood loss and bleeding time in hemophilia A mice model.~~

~~The in vivo activity of SEVENFACT was also assessed in male hemophilia A dogs. Three hemophilia A dogs were dosed by the intravenous route with SEVENFACT at 0.1 mg/kg, two normal dogs were treated with normal saline (NaCl 0.9%) and aPTT, PT, fibrinogen and platelet count were measured pre dose, 10 minutes, and 1, 2, 6 and 24 hours post dosing. The administration of SEVENFACT induced expected pharmacological activity in the hemophilia A dog as a decrease in PT was observed up to 6 hours post dosing (Figure 1).~~

~~Figure 1 Effect of SEVENFACT® on Prothrombin Time~~

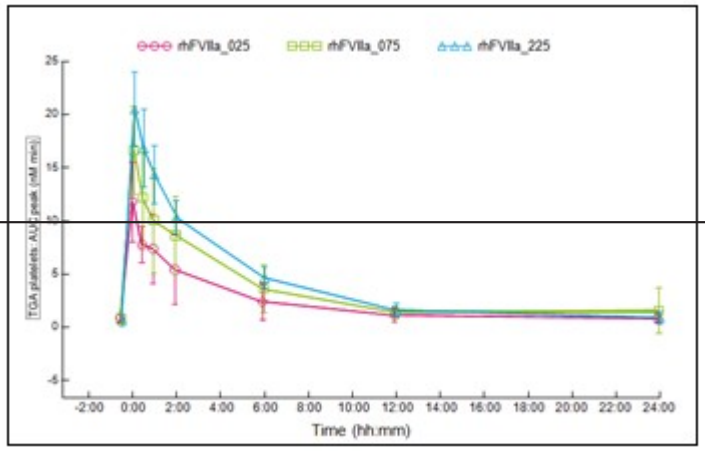


~~The in-vivo activity of SEVENFACT evaluated in a rat venous stasis model at 0.1, 0.3 and 1 mg/kg. Ten animals per dose were treated by intravenous administration. SEVENFACT was pharmacologically active in this model and showed dose-dependent effects on both thrombus score and thrombus weight.~~

~~Human Pharmacodynamic Models~~

~~Clinical pharmacodynamics assessment in a Phase 1b Dose Ranging Study demonstrated a dose and concentration-dependent effect after infusion of rhFVIIa on most of the tested parameters. Specifically for the TGT-assay with platelets, MCF, PT, and aPTT there was a clear relation with the FVIIa activity. Pharmacokinetic/pharmacodynamic analysis shows a saturable relationship between plasma concentrations and coagulation markers (i.e., when concentrations of FVIIa in plasma are at or greater than 1500 ng/mL, coagulation markers levels are at their 80% maximum effect).~~

~~Figure 2 Thrombin Generation Test with Platelets (TGA platelets): AUC of Peak (Mean ± SD)~~

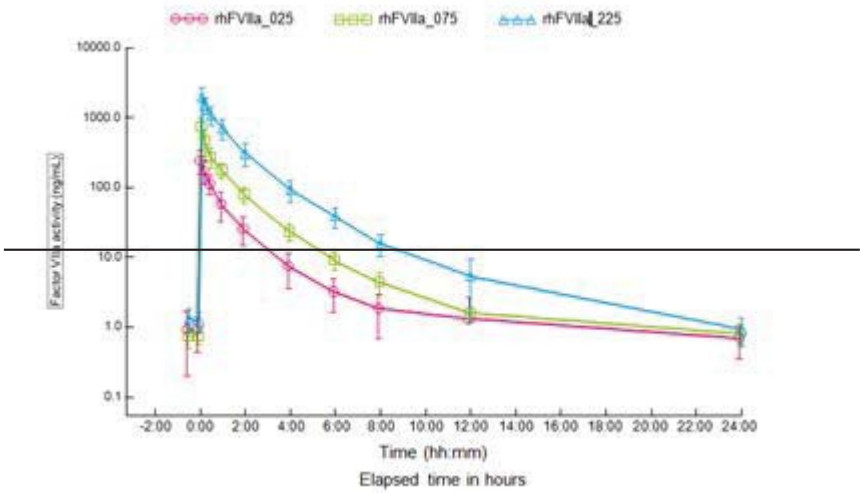


12.4 Pharmacokinetics

~~The pharmacokinetics of SEVENFACT was evaluated in an open-label dose-ranging study in male patients with congenital hemophilia A or B. The objectives were to assess the Pharmacokinetic (PK) and Pharmacodynamic (PD) properties of 3 doses of Coagulation Factor VIIa (Recombinant).~~

~~The study consisted of 3 Cohorts which were dosed in a cross-over manner for repeat administration after a washout period. In Cohort 1, patients initially received 25 µg/kg and in Cohorts 2 and 3 they received 75 µg/kg and 225 µg/kg, respectively. All patients were treated in 2 of the 3 Cohorts. SEVENFACT was administered as an intravenous bolus administration over 2-3 minutes. Sample collection began at 5 minutes post administration and was repeated at several timepoints to permit pharmacologic modeling of SEVENFACT dose response. Recoverable Factor VIIa activity was evaluated and demonstrated significant dose response in Maximum Concentration and AUC. The time to peak FVIIa concentration did not change with the dose as all samples were collected at 5 minutes (Figure 3).~~

~~Figure 3 Factor VIIa Activity, Human Plasma, Hemophilia A and B (semi-log scale, Mean ± SD)~~



~~The increments for $AUC_{0\ inf}$ were dose proportional between the 25 µg/kg and 75 µg/kg groups but slightly more than dose proportional between the 75 µg/kg and 225 µg/kg groups.~~

- ~~Maximum concentration and $AUC_{0\ inf}$ increased with the dose. The increments were dose proportional between the 25 µg/kg and 75 µg/kg groups but slightly more than dose proportional between the 75 µg/kg and 225 µg/kg groups. Half-life was approximately 2 hours in all dose groups.~~

- PK/PD analysis shows a clear relation between rhFVIIa plasma activity levels and clinical coagulation markers (PT, aPTT, RoTEM and TGT with platelets) [see *Clinical Pharmacology (12.2)*].
- For the thrombin generation assay with platelets, MCF (ROTEM FIBTEM), and aPTT, the relationship with rhFVIIa levels was quantified in a population PK/PD model that allowed simulations of dosing scenarios for subsequent studies, and concluded that when concentrations of FVIIa in plasma were at or above 1500 ng/mL, 80% of the maximum effect was achieved. Thus, clinical coagulation markers may not accurately reflect likelihood of achieving hemostasis.

Table 4Single Dose Pharmacokinetic Parameters

PK Parameter (Geometric Mean (CV%))	**C_{max} ng/mL**	**Clearance (mL/h/kg)**	**Vd (L)**	**$t_{1/2}$ (h)**
Dose	**Hemophilia A or B (Age 20 to 61)**			
25 µg/kg (n=10)	230 (43)	9.0 (43)	29.8	2.30
75 µg/kg (n=10)	717 (32)	10.0 (24)	30.4	2.11
225 µg/kg (n=10)	1870 (37)	7.9 (34)	20.0	1.76

In the Phase 1b study, rhFVIIa was shown to be pharmacodynamically active in patients with Congenital Hemophilia A or B. The pharmacokinetic properties for rhFVIIa were determined using both non-compartmental and population PK analyses. Using a population PK approach, clearance from the central compartment was found at 9 L/h, volume of distribution at 13.4 L, and following doses of rhFVIIa of 25, 75 and 225 µg/kg, respectively, $AUC_{0\ inf}$ were found at 207, 635 and 2080 ng*h/mL and C_{max} at 197, 619 and 1960 ng/mL. Results were in the same order of magnitude with NCA, as reported in the table above, with the exception of volume of distribution being higher via NCA. Half-life was approximately 2 hours in all cases. The dose of 25 µg/kg was used as the no-effect or minimal effective dose on coagulation as well as to assess the potential minimal duration of the effective coagulation in order to determine biological efficacy. Further doses of 75 µg/kg (3-fold higher) and the 225 µg/kg (9-fold higher) were administered to examine dose-effect and to determine the onset of coagulation, time to reach the maximal effect, the maximum effect achieved, and the concentration needed to achieve 80% of the maximum pharmacodynamic effect.

12.5Pharmacogenomics

Genotype assessment of hemophilia A or B patients with or without inhibitors was not performed in clinical studies of SEVENFACT.

5 RECOMMENDATIONS

This biological license application is acceptable from clinical pharmacology perspective, with the caveat that resolution of the potency assay related issues doesn't impact the dose accuracy. If dose accuracy is impacted, then a new PK study may be required.

6 APPENDIX

6.1 Individual Studies

6.1.1 Study # 1

Study Title: 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 No. GTC-FVIIa-005-11).

Objectives:
The primary objective of this study was to assess the pharmacokinetic (PK) and pharmacodynamic (PD) properties of 3 doses of Coagulation Factor VIIa (Recombinant) in male congenital Hemophilia A or B patients.

The secondary objective of this study was to assess the safety of 3 doses of Coagulation Factor VIIa (Recombinant) in male congenital Hemophilia A or B patients.

Study Design:
This was a multi-center, randomized, open-label, dose escalation study to assess the pharmacokinetic and pharmacodynamic properties, and the safety of 3 doses of Coagulation Factor VIIa (Recombinant), LR769, in 15 adult male (18 – 75 yeas of age) congenital Hemophilia A or B patients.

As shown in Figure 1, the study consisted of 3 Cohorts. In Cohort 1 patients received 25 µg/kg and in Cohorts 2 and 3 they received 75 µg/kg and 225 µg/kg, respectively. In order to obtain information on the safety of repeat administration of rhFVIIa, all patients were treated in 2 of the 3 Cohorts. Each dose was injected over 2-3 minutes, followed by a 2.5 mL 0.9% saline flush.

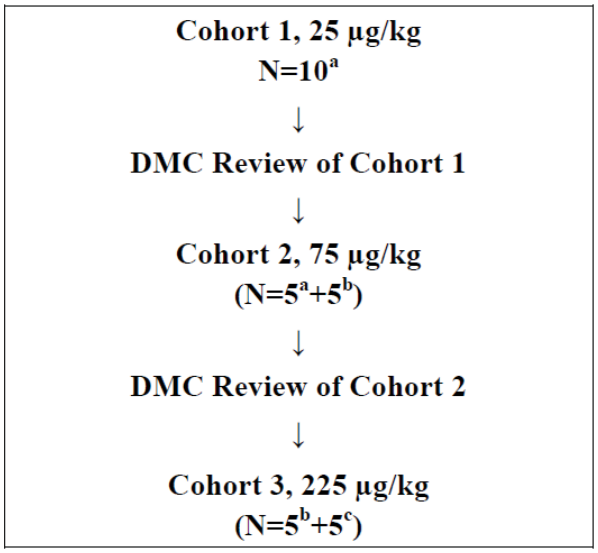


Figure 1 Schematic of Study Design (Source: Applicants Figure 1 in section 5.3.4.2. GTC-FVIIa-005-11: Clinical Study Report, page 23 of 77)

Blood samples for PK assessments were collected at baseline prior to study drug administration, and at 5, 15, 30 minutes, 1, 2, 4, 6, 8, and 12 hours after the start of infusion of study drug. A sample between 24-36 hours post injection was obtained to confirm return to baseline.

Concentrations of FVIIa were determined by a (b) (4) validated (b) (4) assay which uses (b) (4) . PK parameters were calculated from FVIIa levels using non-compartmental PK analysis.

Reviewer's Comments:
In Study # GTC-FVIIa-005-11, in additional to pharmacokinetic assessment for three doses (25 µg/kg, 75 µg/kg and 225 µg/kg), the applicant also evaluated the pharmacodynamics effects of LR769 across the doses. However, per drug product reviewer's comments, the tests used in PD measurements were not sensitive enough for quantitative assessment (please see drug product review for detailed information). Therefore, the PD and PK/PD relationship were not reviewed here.

The pharmacokinetic assessment was directly calculated from blood drug concentrations collected using sufficient sampling schedule. As such, additional submitted population PK

reports are not included in this review, because the regulatory assessment of adequacy study design, PK results, and conclusions is based on the original submitted study reports.

Results

Table 1 shows the pharmacokinetic parameters following a single-dose IV infusion of LR769 manufactured from Process A (small scale). Maximum plasma concentration (Cmax) and area under the curve of LR769 concentration versus time (AUC_{0-t} and AUC_{0-inf}) increased with the dose. The increments appeared to be proportional between the 25 μg/kg and 75 μg/kg groups but slightly more than dose proportional between the 75 μg/kg and 225 μg/kg groups but this should not be considered non-linear pharmacokinetics. The half-life was approximately 2 hours in all dose groups. Factor VIIa activity vs. time is shown in Figure 2.

Table 1 Pharmacokinetic Parameters of LR769 (Process A) (Arithmetic Mean, CV%)

	Arithmetic Mean (CV%)		
Parameters (units)	25 μg/mL	75 μg/mL	225 μg/mL
Cmax (ng/mL)	247.43 (37.70%)	749.96 (32.42%)	1972.95 (34.04%)
AUC_{0-t} (hr*ng/mL)	235.75 (40.97%)	631.06 (27.07%)	2296.82 (28.48%)
AUC_{0-inf} (hr*ng/mL)	256.16 (50.90%)	635.99 (27.02%)	2311.06 (28.38%)
T1/2 (hr)	2.48 (26.17%)	2.16 (23.06%)	1.80 (12.67%)
CL (L/hr)	9.21 (52.31%)	10.25 (21.59%)	8.25 (28.10%)
MRT_{0-last} (hr)	1.81 (58.95%)	1.43 (7.68%)	1.52 (8.17%)
Vss (L)	17.43 (33.27%)	15.84 (26.11%)	13.25 (30.32%)

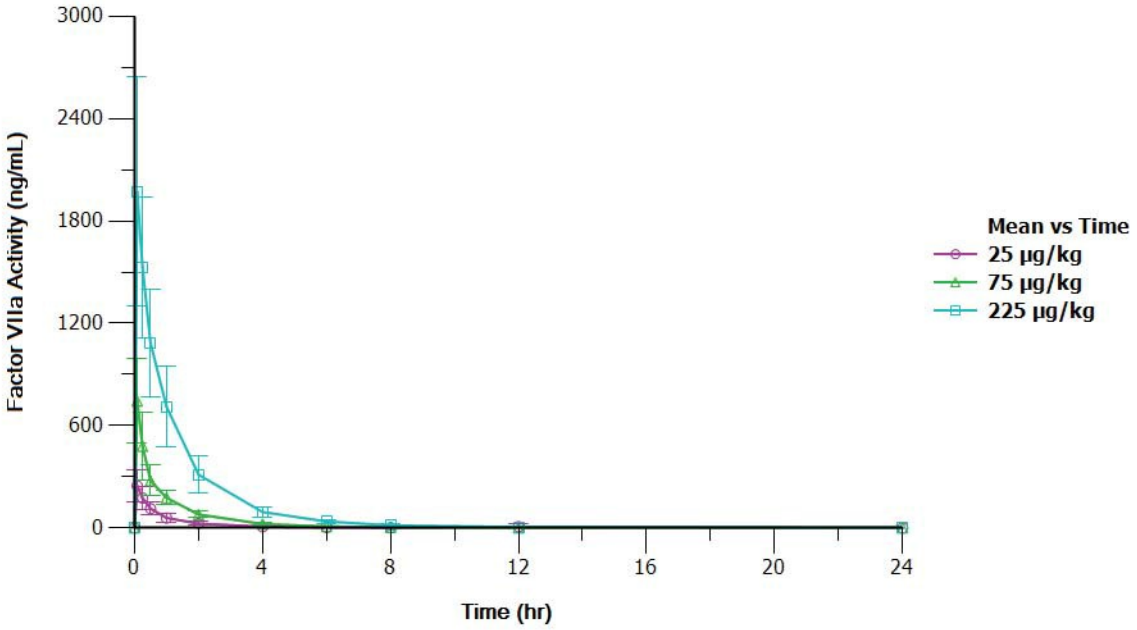


Figure 2. Plasma Factor VIIa Activity versus Time Curve (Mean ± SD)

Conclusions:

For LR769 manufactured via Process A, linear pharmacokinetics were observed after single dose administration in subjects with congenital hemophilia A or B from 25 µg/kg to 225 µg/kg.

6.1.2 Study #2:

Study Title: A Phase 3 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 (Study No. RB-FVIIa-006-13).

Objectives:

Primary Objectives:

- To assess the efficacy of two separate dose regimens (75 μg/kg and 225 μg/kg) of coagulation factor VIIa (recombinant) (LR769) for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII (FVIII) or factor IX (FIX).

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

Secondary Objective:

- To assess the pharmacokinetics (PK) of LR769 (from both Process A and Process B) in hemophilia A or B patients with inhibitors to FVIII or FIX, without a current bleeding episode.

Other Objective:

- To assess the healthcare resource utilization of hemophilia A or B patients with inhibitors treated with LR769.

Study Design:

This was a global, multi-center, phase 3, randomized, open-label, crossover study to assess the dose escalation study to assess safety, pharmacokinetics, and efficacy of coagulation factor VIIa (recombinant) in 27 congenital hemophilia A or B patients with inhibitors to factor VIII or IX.

Subjects were randomized to start one of two treatment regimens: 75 μg/kg or 225 μg/kg. For each treatment regimen, there were 2 phases: Phase A (initial phase) and Phase B (treatment B).

During Phase A, all 27 subjects received a single intravenous (IV) administration of either 75 μg/kg or 225 μg/kg of LR769 (Process A) as a bolus injection within 2 minutes. A subset (n=14) of subjects had samples drawn for PK analysis at specified time points from pre-dose through 8 hours ± 10 minutes post injection.

The investigational drug product, LR769 used in Phase A was produced at the same scale as was used in previous Phase 1b study (Study No. GTC-FVIIa-005-11), Process A LR769. To support product development needs, scale-up and process modifications were applied. Manufacturing of investigational product using Process B was introduced during the study so that some of the

bleeds were treated with Process B product. During Phase B, the starting dose was the same as the dose that patients were randomized to in Phase A.

A bridging PK study (repeat PK study) was conducted using LR769 from Process B after Phase B in the same PK subset of subjects when they were in a non-bleeding state. The dose of LR769 (Process B) was the same as that used in Phase A.

Blood samples for PK assessments were collected at baseline prior to study drug administration, and at 10, 30 minutes, 1, 2, 4, and 8 hours post infusion.

FVIIa concentrations (activity levels) were determined using a validated (b) (4) assay (b) (4) PK parameters were determined by non-compartmental analysis (NCA).

Reviewer's Comments:
In Study #RB-FVIIa-006-13, the pharmacokinetic profiles of Process A & B LR769 were compared. The PK profiles between Process A and Process B LR769 were similar at the dose of 75 μg/kg. However, for the dose of 225 μg/kg, the Cmax and AUC_{0-t} of Process B LR769 were about 75% and 40% higher of Cmax and AUC_{0-t} of Process A LR769, respectively. Safety and efficacy of Process B LR769 have been evaluated. Please refer to the clinical review for detailed information.

The pharmacokinetic assessment was directly calculated from blood drug concentrations collected using sufficient sampling schedule. As such, additional submitted population PK reports are not included in this review, because the regulatory assessment of adequacy study design, PK results, and conclusions is based on the original submitted study reports.

Results:
Comparison of PK parameters between Process A LR769 and Process B LR769 are presented in Table 2 for the two doses of 75 μg/kg or 225 μg/kg.

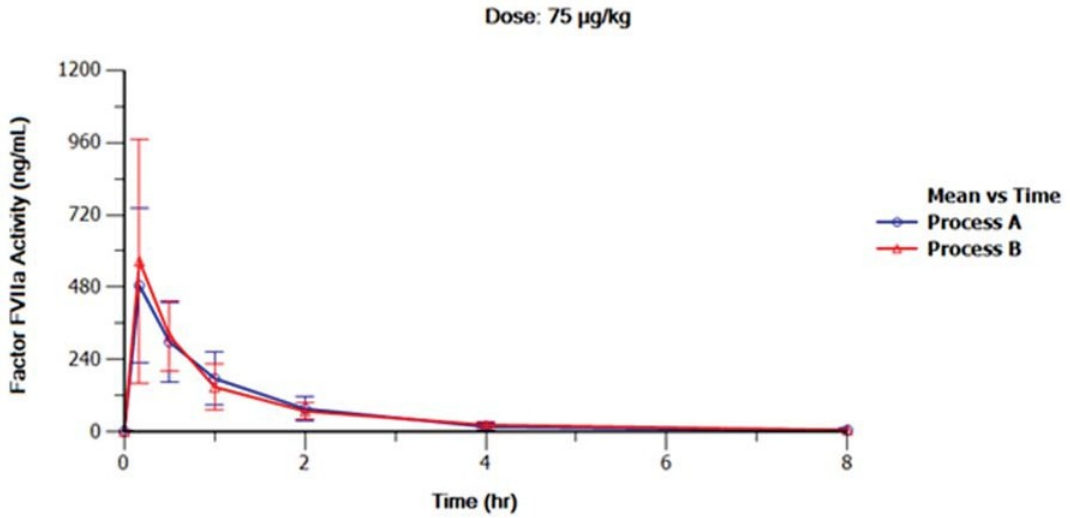
As shown in Figure 3 and Table 2, the PK profiles between Process A and Process B LR769 were similar at the dose of 75 μg/kg. However, for the dose of 225 μg/kg, the Cmax and AUC_{0-t} of Process B LR769 were about 75% and 40% higher of Cmax and AUC_{0-t} of Process A LR769.

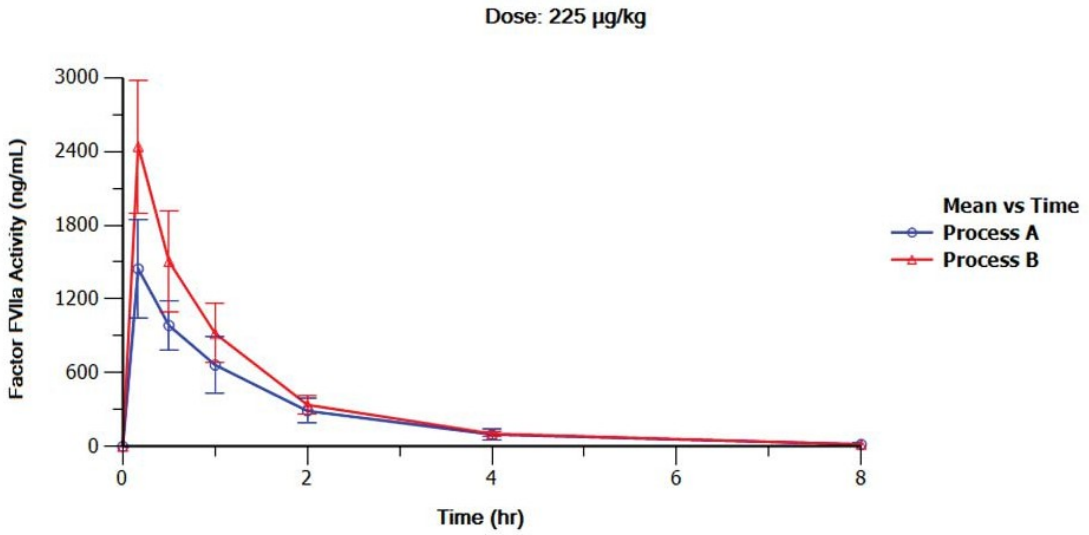
Table 2. Arithmetic Mean Pharmacokinetic Parameters of LR769 Process A & Process B

Study No. RB-FVIIa-06-013 Dose: 75 µg/kg BW									
Parameter (units)	**Process A**				**Process B**				**Process B/ Process A**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC_{0-t} (hr*ng/ml)	557.18	45.30	160.21	824.91	569.48	44.52	229.13	967.04	1.02
AUCoo (hr*ng/ml)	571.01	46.02	162.62	871.18	584.76	43.63	234.75	981.00	1.02
Cmax (ng/ml)	485.14	52.69	200	923	566.16	71.43	215	1354	1.17
Kel (hr^{-1})	0.51	19.48	0.35	0.63	0.41	16.33	0.29	0.48	0.80
T1/2 (hr)	1.41	21.11	1.10	1.94	1.76	18.78	1.43	2.36	1.25

Study No. RB-FVIIa-06-013 Dose: 225 µg/kg BW									
Parameter (units)	**Process A**				**Process B**				**Process B/ Process A**
	Mean	**%CV**	**Min**	**Max**	**Mean**	**% CV**	**Min**	**Max**	
AUC_{0-t} (hr*ng/ml)	1995.95	26.00	1365.99	3015.70	2784.59	20.03	2132.86	3331.12	1.40
AUCoo (hr*ng/ml)	2032.25	25.80	1406.84	3063.37	2820.96	19.83	2161.95	3355.00	1.39
Cmax (ng/ml)	1392.15	29.97	895	2039	2440.60	22.15	1629	3057	1.75
Kel (hr^{-1})	0.53	16.08	0.41	0.64	0.49	11.05	0.41	0.55	0.92
T1/2 (hr)	1.34	16.59	1.09	1.69	1.42	12.05	1.26	1.70	1.06

Figure 3. Plasma Factor VIIa Activity versus Time Curve (Mean ± SD)





Conclusions:

Comparison of pharmacokinetics profiles between Process A & B LR769 showed that:

- The PK profiles between Process A and Process B LR769 were similar at the dose of 75 µg/kg.
- For the dose of 225 µg/kg, the Cmax and AUC0-t for Process B LR769 were about 75% and 40% higher than the Cmax and AUC0-t of Process A LR769, respectively. Based on submitted clinical safety data, no safety signal from Process B 225 µg/kg arm was noted.

Reviewer's Additional Comments:

Currently, based on the CMC review of this submission, it seems that the potency assay may not be accurate and the drug product reviewer is asking to re-evaluate the potency of drug product used in clinical studies based on the revised potency assay. It is possible that the result of the potency re-evaluation may affect the dose accuracy of the pharmacokinetic studies. Therefore, a new PK study maybe required.