CLINICAL PHARMACOLOGY BLA REVIEW

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Office of Tissues & Advance Therapies (OTAT)

STN 125661/0
Sponsor: Bayer Healthcare
Product: PEGylated B-domain deleted (BDD), plasma (b) (4) recombinant factor VIII (BAY 94-9027)
Indication: Controlling and preventing bleeding episodes and for surgical and long term prophylaxis in patients with hemophilia A
Submission Date: August 30, 2017
Reviewer: Iftekhar Mahmood, Ph.D.
RPM: Candace Jarvis
Through: Branch Chief DCEPT, Lei Xu, M.D., Ph.D.

Through: Deputy Division Director DCEPT, Ilan Irony, M.D.

TABLE OF CONTENTS

Introduction 1
Recommendation 3
Study #1: An open-label Phase I trial to evaluate the pharmacokinetics and safety profile of BAY 94-9027 following single and multiple dose administration in two cohorts of previously treated male subjects with severe hemophilia A (PH 36909). 4
Study #2: A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY 94-9027 in severe hemophilia A (PH 38453). 10
Clinical Pharmacology Labeling Comments 13

INTRODUCTION

Antihemophilic factor, PEGylated B-domain deleted (BDD) recombinant Factor VIII (rFVIII) conjugated protein (JIVI) is a sterile, nonpyrogenic, preservative-free, white to slightly yellow lyophilized powder for reconstitution with water as diluent for intravenous (IV) administration. The product is supplied in single use vials containing dosage strengths of (b) (4)

500, 1000, 2000 and 3000 IU in 2.5 ml fill size. The specific activity of JIVI is approximately 10,000 IU/mg protein

The active protein (or starting molecule), prior to conjugation is a recombinant B-domain deleted human coagulation Factor VIII (BDD rFVIII) produced by recombinant DNA technology in baby hamster kidney (BHK) cells. The conjugated protein is prepared without the addition of any human or animal derived protein in the cell culture process, purification, site-specific pegylation or final formulation.

The overall goal of the BAY 94-9027 project was to develop a longer acting FVIII for prophylactic treatment to prevent acute bleeding events in patients with severe hemophilia A. The current approach utilizes site-directed PEGylation to increase the FVIII half-life. Increasing the FVIII half-life is expected to result in a longer duration in effect by maintaining plasma trough levels (b) (4) for longer duration thereby, allowing for less frequent dosing when used in a prophylaxis setting.

RECOMMENDATION

From clinical pharmacology perspective, the PK study design and analysis of BAY 94-9027 in subjects with severe hemophilia A is acceptable. The clinical pharmacology labeling should be revised as proposed by the FDA.

Study #1

Study title: An open-label Phase I trial to evaluate the pharmacokinetics and safety profile of BAY 94-9027 following single and multiple dose administration in two cohorts of previously treated male subjects with severe hemophilia A (PH 36909).

This was a multi-center, non-randomized, open label, parallel group study. The objectives of the study were as follows:

- To assess the pharmacokinetics of BAY 94-9027 following intravenous administration of a single and repeat doses of BAY 94-9027.
- To assess the safety and immunogenicity of BAY 94-9027 administered over a period of 8 weeks.

BAY 94-9027 was given to subjects with severe hemophilia A in two separate cohorts (low dose and high dose).

Low dose cohort - Cohort 1:

Single dose: 25 IU/kg BAY 94-9027
Multiple dose: 25 IU/kg BAY 94-9027 twice weekly

High dose cohort - Cohort 2:

Single dose: 60 IU/kg BAY 94-9027
Multiple dose: 60 IU/kg BAY 94-9027 once weekly

Duration of treatment:

Low dose cohort:

One exposure day to Kogenate FS® (25 IU/kg) followed by 72-hours washout period
Sixteen exposure days to BAY 94-9027 (25 IU/kg) over a period of 8 weeks

High dose cohort

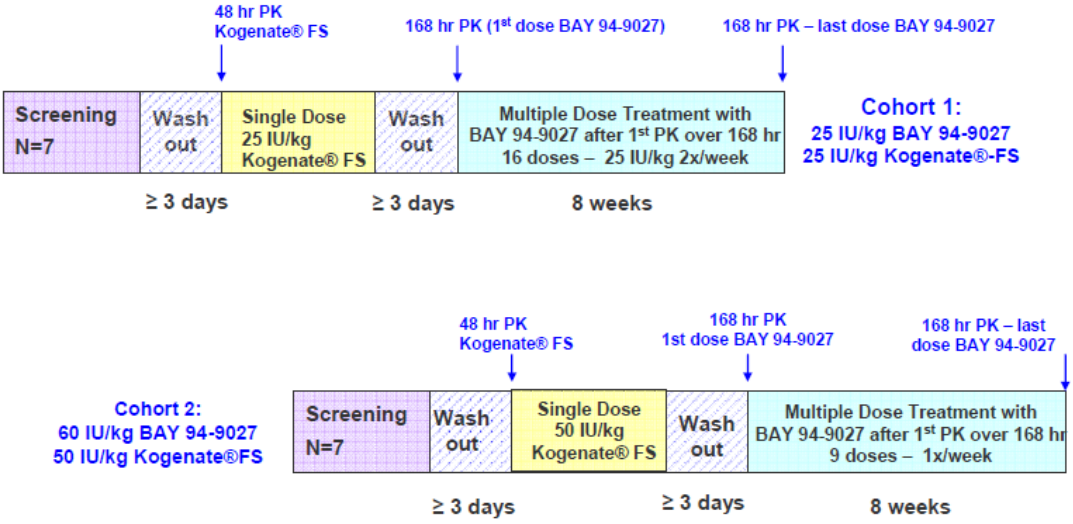
One exposure day to Kogenate FS (25 IU/kg) followed by 72-hours washout period
Nine exposure days to BAY 94-9027 (60 IU/kg) over a period of 8 weeks

Reference drug: Kogenate FS (Intravenous administration)
Low dose: single dose 25 IU/kg Kogenate FS
High dose: single dose 50 IU/kg Kogenate FS

The subjects in the low dose cohort received a single dose of 25 IU/kg Kogenate FS, followed by a washout period of at least 72 hours following their last FVIII injection. After that a PK study

of Factor VIII (FVIII) was conducted. After another washout period of at least 72 hours, the subjects received a single dose of 25 IU/kg BAY 94-9027, after which FVIII levels were assessed over 7 days and compared to those observed following Kogenate FS. After 7 days, multiple dosing of BAY 94-9027 began and continued for a total of 8 weeks (last dose at the end of the 8th week). Following the last scheduled dose of BAY 94-9027, FVIII levels were measured for 7 days and compared with those measured after the first dose of BAY 94-9027.

The subjects in the high dose cohort received a single dose of 50 IU/kg Kogenate FS, followed by a washout period of at least 72 hours. Then, the subjects received a single dose of 60 IU/kg BAY 94-9027, followed a week later by once weekly injections at of 60 IU/kg BAY 94-9027 for 8 weeks. The schematic study design is shown below.



On days when blood samples for pharmacokinetic (PK) analyses were obtained, study drug was administered at the site, the dose was injected over a 10-minute period. On days when the subject self-infused, the subject was instructed to deliver the injection over a 5 to 10-minute period.

Subjects were all males, between 18-65 years of age (mean age = 36 years), and had severe hemophilia A (plasma baseline Factor VIII level <1 %). Subjects had a minimum of 150 days of previous exposure with a Factor VIII concentrate(s) and had to be immunocompetent as measured by a CD4+ lymphocyte count >400/mm^3. A total of 14 subjects participated in this study, equally distributed between 2 cohorts (7 subjects in each cohort).

Blood samples for PK analysis were taken at time 0 (pre-infusion), 0.25, 0.5, 1, 3, 6, 8, 24, 48, 72, (96-144), and 168 hours following Kogenate FS and BAY 94-9027 (same time points for a single and multiple dose). Three methods (chromogenic, one-stage assay and (b) (4) assay) were used to measure the plasma concentrations following BAY 94-9027 and two methods (chromogenic and one-stage assay) were used to measure the plasma concentrations following

Kogenate FS. Pharmacokinetic parameters of Kogenate FS and BAY 94-9027 were estimated by non-compartmental analysis and are summarized in Tables 1-4.

Table 1: Pharmacokinetic parameters (mean ± sd) following a single dose of Kogenate FS (25 IU/kg) and a single and multiple dose of BAY 94-9027 (chromogenic assay)

PK parameters	**Low Dose 25 IU/kg**		
	Kogenate FS Single dose	BAY 94-9027 Single dose	BAY 94-9027 Multiple dose
C_{max} (IU/dL)	72 ± 18	64 ± 9	80 ±11
AUC (IU*hr/dL)	1212 ± 553	1638 ± 50	2112 ± 638
CL (mL/h/kg)	2.5 ± 1.2	1.7 ± 0.4	1.3 ± 0.3
Half-life (hrs)	13 ± 4	19 ± 6	19 ± 6
MRT (hrs)	19 ± 5	27 ± 7	28 ± 9
Vss (mL/kg)	430 ± 130	428 ± 50	335 ± 34

Following a single low dose (25 IU/kg) of BAY 94-9027, the AUC was higher by 35%, CL was slower by 32% and half-life was longer by 45% as compared to Kogenate FS (Table 1). Multiple dosing of BAY 94-9027 led to an increase in AUC by approximately 30% and a reduced clearance of 25%. The half-life of BAY 94-9027 was comparable between single and multiple dose (Table 1).

Table 2: Pharmacokinetic parameters (mean ± sd) following a single dose of Kogenate FS (50 IU/kg) and a single and multiple dose of BAY 94-9027 (chromogenic assay)

PK parameters	**High Dose 60 IU/kg**		
	Kogenate FS Single dose	BAY 94-9027 Single dose	BAY 94-9027 Multiple dose
C_{max} (IU/dL)	238 ± 76	176 ± 45	187 ± 34
AUC (IU*hr/dL)	2653 ± 1080	4553 ± 1813	4892 ± 1458
CL (mL/h/kg)	2.0 ± 0.6	1.4 ± 0.4	1.3 ± 0.3
Half-life (hrs)	13 ± 2	19 ± 3	20 ± 4
MRT (hrs)	18 ± 3	20 ± 4	27 ± 4
Vss (mL/kg)	365 ± 90	386 ± 66	343 ± 50

Following a single high dose (60 IU/kg) of BAY 94-9027, the AUC was higher by 72%, CL was slower by 30% and half-life was longer by 45% as compared to Kogenate FS (Table 2). Clearance, AUC, and half-life were comparable between single and multiple dose of BAY 94-9027 (Table 2).

Based on chromogenic (b) (4) assay, the half-lives of BAY 94-9027 were comparable with the chromogenic assay for both 25 IU/kg and 60 IU/kg dose. Clearance of BAY 94-9027 was higher by (b) (4) assay than chromogenic assay by 18% and 36% for 25 IU/kg and 60 IU/kg dose, respectively.

Table 3: Pharmacokinetic parameters (mean ± sd) following a single dose of Kogenate FS (25 IU/kg) and a single and multiple dose of BAY 94-9027 (one-stage assay)

PK parameters	Low Dose 25 IU/kg		
	Kogenate FS Single dose	BAY 94-9027 Single dose	BAY 94-9027 Multiple dose
C_{max} (IU/dL)	60 ± 20	69 ± 11	99 ± 29
AUC (IU*hr/dL)	971 ± 616	1644 ± 663	2131 ±822
CL (mL/h/kg)	3.3 ± 1.6	1.7 ± 0.5	1.3 ± 0.4
Half-life (hrs)	14 ± 5	21 ± 13	21 ± 9
MRT (hrs)	20 ± 7	29 ± 14	29 ± 11
Vss (mL/kg)	590 ± 210	447 ± 54	346 ± 73

Following a single low dose (25 IU/kg) of BAY 94-9027, the AUC was higher by 70%, CL was slower by 50% and half-life was longer by 50% as compared to Kogenate FS (Table 3). Multiple dosing of BAY 94-9027 led to an increase in AUC by approximately 30% and a reduced clearance of 25%. The half-life of BAY 94-9027 was comparable between single and multiple dose (Table 3).

Table 4: Pharmacokinetic parameters (mean ± sd) following a single dose of Kogenate FS (50 IU/kg) and a single and multiple dose of BAY 94-9027 (one-stage assay)

PK parameters	High Dose 60 IU/kg		
	Kogenate FS Single dose	BAY 94-9027 Single dose	BAY 94-9027 Multiple dose
C_{max} (IU/dL)	212 ± 36	269 ± 117	242 ± 63
AUC (IU*hr/dL)	2159 ± 379	4490 ± 1005	4794 ± 1351
CL (mL/h/kg)	2.4 ± 0.5	1.4 ± 0.3	1.3 ± 0.4
Half-life (hrs)	13 ± 2	17 ± 1	20 ± 6
MRT (hrs)	17 ± 3	24 ± 2	26 ± 5
Vss (mL/kg)	400 ± 7	330 ± 60	334 ± 56

Following a single high dose (60 IU/kg) of BAY 94-9027, the AUC was higher by more than 100%, CL was slower by 40% and half-life was longer by 30% as compared to Kogenate FS (Table 4). Clearance, AUC, and half-life were comparable between single and multiple dose of BAY 94-9027 (Table 4).

Mean plasma concentrations vs time profiles of Kogenate FS and BAY 94-9027 are shown in Figures 1-2.

Figure 1: Mean plasma concentrations vs time profile following a single dose of 25 IU/kg Kogenate FS and BAY 94-9027 from Cohort 1 based on chromogenic and one-stage assay

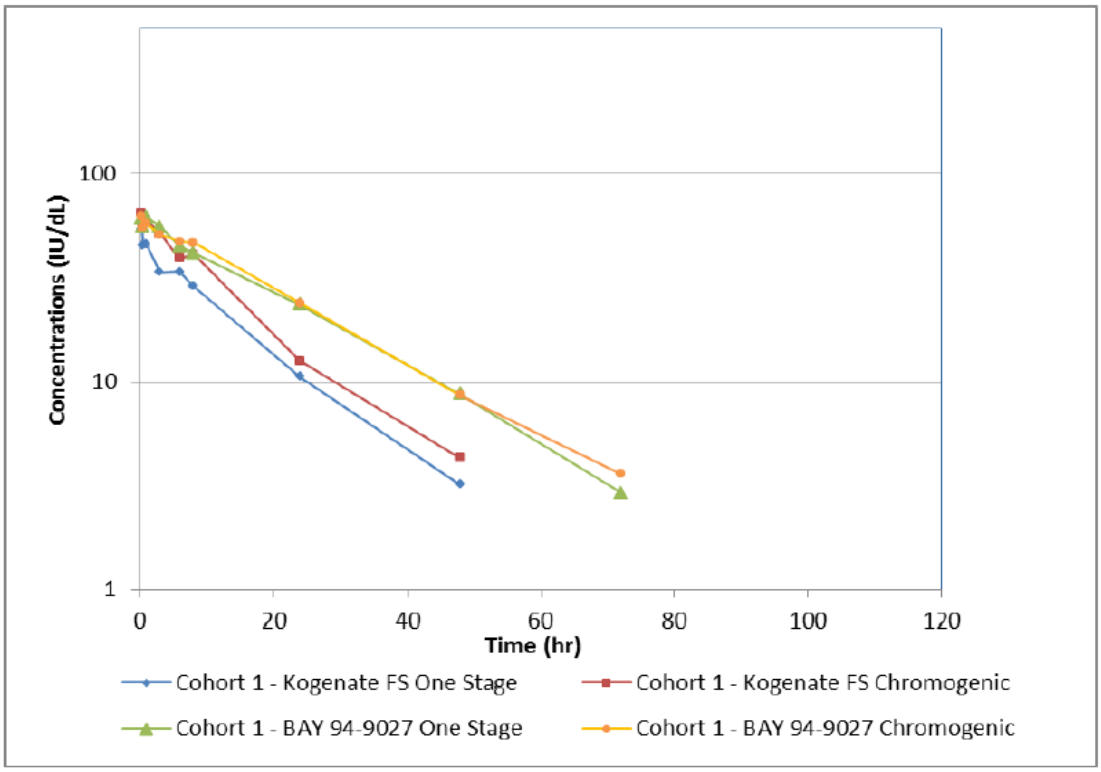
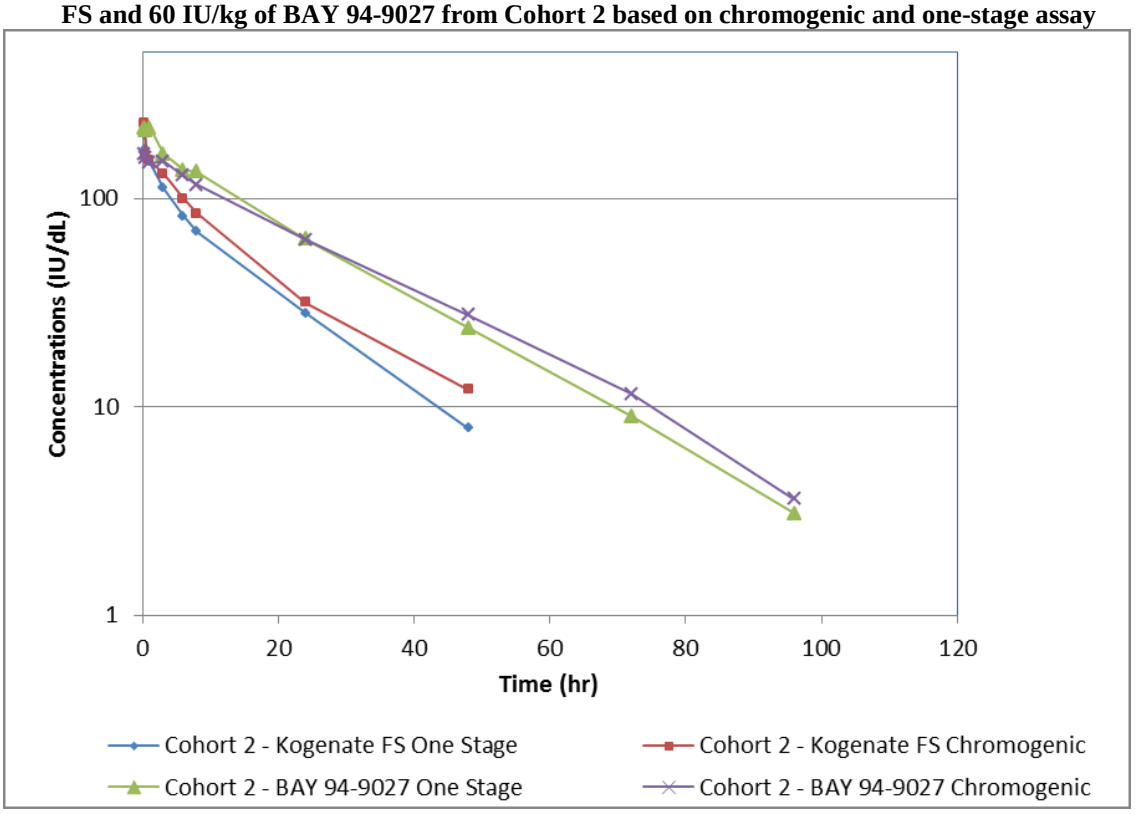


Figure 2: Mean plasma concentrations vs time profile following a single dose of 50 IU/kg Kogenate FS and 60 IU/kg of BAY 94-9027 from Cohort 2 based on chromogenic and one-stage assay



Conclusions: Compared with Kogenate FS, BAY 94-9027 has higher exposure and lower clearance. The AUC of BAY 94-9027 increased proportionally from 25 IU/kg to 60 IU/kg dose. The half-life of BAY 94-9027 was longer by 6-7 hours than Kogenate. Multiple dosing of BAY 94-9027 did not lead to accumulation in plasma.

Study #2

Study title: A Phase II/III, multicenter, partially randomized, open label trial investigating safety and efficacy of on-demand and prophylactic treatment with BAY 94-9027 in Severe Hemophilia A (Report no. PH-38453).

This was a multicenter, multinational, partially randomized, open-label trial with four treatment subgroups evaluating the safety and efficacy of a PEGylated B-domain deleted (BDD), plasma protein-free, recombinant factor VIII (BAY 94-9027) in previously treated adults and adolescents with severe hemophilia A. There were two parts of the study and are described below.

Part A:

The objective of this part of the study was to assess long term safety of BAY 94-9027 over at least 100 accumulated exposure days (ED). In this part of study, there were 121 subjects (12-65 years of age) with severe hemophilia A who had completed the Part A main trial. Subjects who signed consent for the Part A extension were given a ±1week grace period to switch from on-demand to prophylaxis or to another dosing regimen within the prophylaxis group. No pharmacokinetic (PK) study was conducted in Part A of the study.

Part B Extension: Major surgery using BAY 94-9027:

The objective of this part of the study was to assess the safety and efficacy of BAY 94-9027 in the prevention of bleeding during major surgical procedures. All subjects participating in Part B were required to undergo PK assessment in order to determine the appropriate dose and dosing frequency during their surgical procedure. PK study was conducted 24 hours before surgery. Subjects were administered a dose of 50 IU/kg BAY 94-9027 by intravenous infusion over 15 minutes. Blood samples were collected at pre-infusion, 15 min, 1, 3, 6 to 8, and 24-hours post infusion. Blood samples for subjects who underwent surgery were taken at pre-infusion, between 6 to 8 hours, and at 24 hours or immediately prior to next dose of BAY 94-9027.

A total of 18 subjects underwent surgery. For 15 subjects, pre-surgery PK was conducted in Part B and PK parameters were assessed for 14 subjects. One subject did not have ample blood samples for the estimation of PK parameters. For the other 3 subjects, the PK from Part A was available so another PK study was not conducted in these 3 subjects.

The PK parameters of BAY 94-9027 in patients with severe hemophilia A prior to surgery are shown in Table 1. PK parameters in patients after surgery could not be evaluated due to sparse blood sampling.

The AUC of BAY 94-9027 is based on concentrations measured from time 0 to 24 hours and was not extrapolated to infinity because the tail portion of the AUC contributed substantially (68% for one-stage assay and 56% for chromogenic assay) to the total AUC. This resulted in substantial increase to the clearance of BAY 94-9027 compared with the previous study (PH

36909) where blood samples were taken till 168 hours. Furthermore, the half-life of BAY 94-9027 should be interpreted cautiously due to blood sampling till 24 hours.

Table 1: Pharmacokinetic parameters of BAY 94-9027 prior to surgery (n = 14)

Parameters	One-Stage assay	Chromogenic assay
C_{max} (IU/dL)	163 ± 68	154 ± 59
$AUC_{(0-24)}$ (IU*hr/dL)	2014 ± 686	2044 ± 628
CL (mL/h/kg)	2.9 ± 1.5	2.7 ± 0.8
Half-life (hrs)	18 ± 7	16 ± 5

Conclusions: The PK of BAY 94-9027 has not been well characterized in this study due to inadequate blood sampling scheme (24 hours). Although, the Applicant claims that the dose of BAY 94-9027 to the surgical patients was selected based on individual patient's PK, it is highly likely that other factors besides an individual's PK were also incorporated into the dosing of BAY 94-9027 in surgical patients (please see below).

In an information request, the applicant was asked the following:
You selected individual dose of BAY 94-9027 in patients who underwent surgery based on PK study before surgery. Please provide your method of dose selection based on PK study in the patients.

Bayer Response:
The Study 13024 protocol v4 Section 6.1.3 stated that a loading dose of 50 IU/kg (or as determined by individual PK) given ≤60 min before start of procedure and 15 to 50 IU/kg repeated as indicated in the per-surgical period. This guidance was based on known behavior of FVIII. It was expected that the doses required for maintaining hemostasis during surgical interventions would be similar to those of other FVIII products with the only expected difference being the dosing intervals due to the extended half-life of BAY 94-9027. In accordance with local standard of care, the treating physician had primary responsibility for determining the doses and the frequency of infusion, and these decisions would be guided by the PK results obtained prior to the procedure using local laboratory results. In all cases, patients undergoing surgery were expected to be treated according to the type of procedure, using doses expected to provide acceptable therapeutic levels of FVIII activity based on the pre-surgical measurements and any additional monitoring in the clinical setting. The appropriate treatment of surgery was at the discretion of the treating physician, local clinical practice, and could be extrapolated from published guidelines (*e.g.* World Federation of Hemophilia).

Overall the data from the 20 surgeries show that the efficacy of BAY 94-9027 in surgical setting was proven by good or excellent hemostasis during surgery. The first dose administered at the start of the surgery was about 50 IU/kg as per the protocol and was comparable to other FVIII

products. The median time between the pre-surgery and the next infusion was ~ 12 hrs. Majority of the patients required additional injections at 12-24 h interval from day 2 onwards.

CLINICAL PHARMACOLOGY LABELING COMMENTS

12.1 Mechanism of Action

The description of mechanism of action is inadequate. Please re-write.

~~JIVI exhibits an extended terminal half-life ($t_{1/2}$) and an increased AUC through pegylation compared to KOGENATE FS *[see Clinical Pharmacology (12)]*. Pegylation in the A3 domain reduces clearance of Factor VIII while maintaining the normal functions of the B-domain deleted rFVIII molecule.~~

12.3 Pharmacokinetics

In Table 4, please also provide PK parameters of JIVI following 25 IU/kg dose.

Table 4: Pharmacokinetic Parameters (Arithmetic Mean ± SD) for JIVI following a Single 60 IU/kg Dose based on Chromogenic and One-stage assay

PK parameter (unit)	**Chromogenic assay N=22**	**One-stage assay N=22**
AUC (IU*h/dL)	3900 ± 1280	4040 ± 1080
~~**AUC_{norm} (kg*h/dL)**~~	~~65.7 ± 21.4~~	~~68.1 ± 18.1~~
C_{max} (IU/dL)	164 ± 23.8	195 ± 37.0
~~**$C_{max,norm}$ (kg/dL)**~~	~~2.77 ± 0.396~~	~~3.29 ± 0.648~~
$t_{½}$ (h)	17.6 ± 4.26	17.7 ± 4.27
MRT_{IV} (h)	25.2 ± 6.19	24.9 ± 6.19
V_{ss} (dL/kg)	0.396 ± 0.0631	0.371 ± 0.0632
CL (dL/h/kg) change to mL/hr/kg	0.0168 ± 0.00553	0.0157 ± 0.00408

AUC: area under the curve; AUC_{norm}: AUC normalized; C_{max}: maximum drug concentration in plasma after single dose; $t_{½}$: terminal half-life; MRT_{IV}: mean residence time after an IV administration; V_{SS}: apparent volume distribution at steady-state; CL: clearance

Please provide this information in Table 4

The median overall Factor VIII recovery values were 2.6 kg/dL (range: 1.3 to 4.5 kg/dL) using the chromogenic assay and 2.8 kg/dL (range: 1.2 to 4.9 kg/dL) using the one-stage assay.

Delete Table 5 because POPPK does not provide any additional information over non-compartmental analysis.

A population PK model was developed based on measurements (from dense PK sampling and all recovery samples) throughout the 3 clinical studies (N=206). Table 5 below provides PK parameters based on the population PK model.

Table 5: PK Parameters [Geometric Mean (%CV)] based on Population PK Estimated Dose of 60 IU/kg, Using Chromogenic Assay

PK parameter (unit)	12 to <18 years N=12	≥18 years N=133	Total (≥12 years) N=145
AUC (IU*h/dL)	3341 (34.2)	4050 (31.1)	4000 (31.6)
AUC_{norm} (kg*h/dL)[a]	57.4 (32.6)	67.5 (30.6)	66.6 (31.0)
$t_{1/2}$ (h)	16.8 (25.2)	17.5 (28.8)	17.4 (28.4)
V_{ss} (dL/kg)	0.423 (15.5)	0.373 (15.6)	0.376 (15.9)
CL (dL/h/kg)	0.0174 (34.2)	0.0148 (31.1)	0.0150 (31.6)

[a] AUC_{norm} calculated for a dose of 60 IU/kg