

CLINICAL PHARMACOLOGY BLA REVIEW

Division of Hematology
Office of Blood Review & Research

BLA 125444/0

Product: recombinant coagulation factor IX Fc fusion protein (rFIXFc, ALPROLIX™)

Sponsor: Biogen Idec

Indication: For the treatment of hemophilia B indicated in adults and children (> 2 years)

Date Received: January 08, 2013

Reviewer: Carl-Michael Staschen, M.D., Ph.D.

RPM: Edward Thompson

Through: Iftekhar Mahmood Ph.D. and Basil Golding, M.D.

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Studies reviewed:

Study #1: A Phase 1/2a safety and pharmacokinetic study of intravenous rFIXFc in previously treated hemophilia B patients (Study No. SYN-FIXFc-0007-01)

Study #2: An open-label, multi-center evaluation of the safety, pharmacokinetics, and efficacy of recombinant, long-acting coagulation factor IX Fc fusion protein (rFIXFc) in the prevention and treatment of bleeding in previously treated subjects with severe hemophilia B (Study Number: 998HB102)

Study #3: A population pharmacokinetic analysis of rFIXFc in patients with severe hemophilia B (Report No. -----(b)(4)-----).

Study #4 (Interim Report): An open-label, multicenter evaluation of safety, pharmacokinetics, and efficacy of recombinant coagulation factor IX Fc fusion protein, ---(b)(4)--, in the prevention and treatment of bleeding episodes in pediatric subjects with hemophilia B. (Study Number: 9HB02PED)

EXECUTIVE SUMMARY

Background:

Hemophilia B is a deficiency in the clotting factor IX (FIX) and is a recessively inherited coagulation disorder due to an X-chromosome mutation carried by females and expressed mainly by males affecting approximately 80,000 people worldwide. There is no available cure for hemophilia B. To promote clotting, treatment focuses on the replacement of FIX with intravenous (IV) administration of FIX-containing coagulation products that are either plasma-derived (pdFIX) or recombinant-derived (rFIX). One major limitation of rFIX is its short half-life, with a mean of 18 to 22 hours.

Biogen Idec is developing rFIXFc (ALPROLIX™) which is a recombinant fusion protein composed of FIX attached to the Fc domain of human IgG1. rFIXFc comprises a single FIX genetically linked to the Fc domain of human IgG with no intervening linker sequences. The rFIXFc drug substance is produced in human embryonic kidney -----(b)(4)----- cells. rFIXFc has been designed to be a long-acting version of FIX.

Proposed Indication

Biogen Idec is seeking approval for its recombinant FIX fusion protein (rFIXFc, ALPROLIX™) for the following indication:

The long acting anti-hemophilic factor (recombinant) rFIXFc is indicated in adults and children (≥ 2 years old) with hemophilia B (congenital FIX deficiency) for:

- Control and prevention of bleeding episodes.
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Perioperative management (surgical prophylaxis)

The following is the summary of the 4 submitted PK studies.

Assay methodology and PK analysis

PK concentration-profile in all studies were determined based on the disposition of plasma FIX activity over time as measured by a validated one-stage activated partial thromboplastin time (aPTT) clotting assay. The PK data analyses was performed using either noncompartmental or compartmental analyses

Results

1. The Phase 1/2a trial was an open-label, multi-center, safety, dose-escalation study (14 previously treated patients (PTP, >18 y) with severe hemophilia B). Ascending single doses (12.5-100 IU/kg) of rFIXFc were given as an IV-infusion over 10 minutes. The estimated mean clearance (mL/kg/h) of rFIXFc ranged from 3.44 (50 IU/kg) to 2.84 (100 IU/kg) and the mean elimination half-life (h) ranged from 57.6 (50 IU/kg) to 56.5 (100 IU/kg).

2. The Phase 3 study was an open-label, multicenter study to evaluate the safety, tolerability, PK, and efficacy of rFIXFc administered as an IV infusion in PTPs (≥ 12 y) with severe hemophilia B. A total of 120 subjects had PK assessments and periodic trough/peak measurements were done during the study. A PK subgroup received sequential single IV doses of 50 IU/kg BeneFIX® (competitor) and rFIXFc for direct comparison of detailed PK profiles. The mean incremental recovery (IR) (IU/dL per IU/kg) of rFIXFc was 0.87 after a dose of 50 IU/kg and 1.02 hours after 100 IU/kg. Mean clearance of rFIXFc was estimated to be 3.46 mL/h/kg after a dose of 50 IU/kg and 2.65 mL/h/kg after 100 IU/kg. The mean elimination half-life of rFIXFc was 75 hours after a dose of 50 IU/kg and 101 hours after 100 IU/kg. The PK profiles and estimated parameters of adolescents were similar to adults. Compared to the competitor BeneFIX®, rFIXFc showed a 2.4-fold longer elimination half-life.

3. Combining PK data from the clinical Phase 1/2 and Phase 3 studies, a nonlinear mixed effects model (population) PK analysis was performed to describe the disposition of rFIXFc. Overall, the estimated PK parameters of rFIXFc derived from a 3-compartment population PK model are consistent with the results from the 2-compartment model in the conventional PK analysis, suggesting that the contribution of the third compartment to rFIXFc PK was minimal. The following statements summarize the analysis:

- The impact of body weight (BW) on clearance and central volume of distribution is limited, and simulation results indicate that both BW-based and fixed dosing are feasible approaches for treating hemophilia B patients of 12 years and older.
- Simulations for prophylaxis predict that 50 IU/kg (or 4000 IU) once weekly, or 100 IU/kg (or 8000 IU) every 10-14 days would maintain FIX activity within 1-150% in the majority of the population.
- Surgical procedures performed in phase 3 study did not alter rFIXFc disposition.
- No clinically significant impact of anti-drug-antibody (4 subjects) on the PK of rFIXFc.

4. The ongoing pediatric study (9HB02PED) is an open-label, multicenter evaluation of the safety, PK, and efficacy of rFIXFc for routine prophylaxis in pediatric PTPs with severe hemophilia B. Eighteen pediatric subjects (5 subjects 2 to <6 years of age and 13 subjects 6 to <12 years of age) had evaluable rFIXFc PK profiles. The following conclusions can be drawn from this study:

- Compared to adults, there is a substantial relative decrease in mean incremental recovery (IR) = -41% and a relative increase in mean bodyweight adjusted CL = +39% in pediatric patients 2 to <6 years of age. These differences should be taken into account when dosing children 2 to <6 years of age.
- Consistent across all age groups, rFIXFc is observed to have a prolonged $T_{1/2}$ and reduced CL compared with other FIX products.

OVERALL COMMENTS

- In general, the results of the PK analyses and conclusions are acceptable from a Clinical Pharmacology perspective.
- In the population PK study simulations for prophylaxis predicted that at a dose of 100 IU/kg of rFIXFc every 10 days more than 85% of the population was within the range of 1% to 150%. However, simulations of 100 IU/kg of rFIXFc every 14 days predicted only more than 50% of the population within the range of 1% to 150%. Based on these results a dosing regimen of 100 IU/kg every 14 days is not acceptable, because nearly 50% of the patients will be under dosed. To achieve and sustain therapeutic concentrations in the majority of patients a dosing frequency of every 10 days appears to be sufficient.
- A final assessment of the pediatric PK study can only be made after submission of the final study report.

CLINICAL PHARMACOLOGY LABELING COMMENTS

Page 1: Use In Specific Population.

Pediatric: Safety, efficacy, and pharmacokinetics of ALPROLIX have been evaluated in previously treated pediatric patients (PTP) ages 12 years and older. No dose adjustment is required. In pediatric patients less than 12 years of age, recovery may be lower and **bodyweight adjusted** clearance may be higher, potentially requiring dose adjustment. (8.4)

Page 1: -----DOSAGE AND ADMINISTRATION-----

For Intravenous Use after Reconstitution only (2)

- For prophylaxis regimen to prevent or reduce frequency of bleeding episodes, dose at either 50 IU/kg once weekly or 100 IU/kg once every 10–14 days. Either regimen may be adjusted based on individual response. (2.4)

2.4 Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B

The recommended starting regimens are either:

- 50 IU/kg once weekly
- OR
- 100 IU/kg once every 10–14 days

Either regimen may be adjusted based on individual response [*see Pharmacokinetics (12.3)*].

8.4 Pediatric Use

Safety, efficacy, and pharmacokinetics of ALPROLIX have been evaluated in previously treated pediatric patients 12 years of age and older and no dose adjustment is required.

In comparison with adolescents and adults, children less than 12 years of age may have higher factor IX **bodyweight adjusted** clearance, shorter half-life, and lower recovery. These differences should be taken into account when dosing. Higher doses **per kg bodyweight** or more frequent dosing may be needed in patients less than 12 years of age. [*see Clinical Pharmacology (12.3)*]

Use of ALPROLIX in children less than 12 years of age is supported by evidence from ~~the adequate and well-controlled study of ALPROLIX in subjects 12 years of age and older (phase 3 study)~~ and additional interim pharmacokinetic data from a study of pediatric subjects ~~less than 12 years of age~~. [*see Clinical Pharmacology (12.3)*]

Section 12.3 Pharmacokinetics

Comment: the complete subsection “Pharmacokinetic Properties” should be deleted and replaced, because labeling information should only focus on the sponsor’s submitted drug product and not on the drug of the competitor.

Pharmacokinetic Properties

The pharmacokinetics (PK) of ALPROLIX (rFIXFe) versus BeneFIX (rFIX) were evaluated following a 10-minute IV infusion in 22 evaluable subjects from a clinical study. The subjects underwent a washout period of 5 days prior to receiving 50 IU/kg of BeneFIX. PK sampling was conducted pre-dose followed by assessments at 8 time points up to 96 hours post-dose. Following a washout period of 120 hours (5 days), the subjects received a single dose of 50 IU/kg of ALPROLIX. PK samples were collected pre-dose and then subsequently at 11 time points up to 240 hours (10 days) post-dose. A repeat PK evaluation of ALPROLIX was conducted at Week 26.

PK parameters for ALPROLIX were estimated based on the plasma FIX activity over time profile. For ALPROLIX, the maximum activity (C_{max}) was observed immediately following infusion, e.g., at 10 minutes from the start of the dosing. The geometric mean increase in circulating FIX activity from pre-infusion level was 0.92 IU/dL per IU/kg and the elimination half-life was 82 hours. This half-life is influenced by the Fe region of ALPROLIX, which in animal models was shown to be mediated by the FeRn cycling pathway. The ALPROLIX PK profile was stable over repeated dosing as shown by comparable PK parameters at Week 26.

A summary of PK parameters for ALPROLIX and BeneFIX are presented in Table 4.

Table 4: Pharmacokinetic Parameters of ALPROLIX(rFIXFe) and BeneFIX (rFIX)

PK Parameters [†]	ALPROLIX (95% CI)	BeneFIX (95% CI)	Ratio of ALPROLIX to BeneFIX (95% CI)
-	N=22	N=22	N=22
C_{max} (IU/dL)	40.81 (33.60, 49.58)	43.08 (36.69, 50.59)	0.95 (0.81, 1.11)
AUC/Dose (IU*h/dL per IU/kg)	31.32 (27.88, 35.18)	15.77 (14.02, 17.74)	1.99 (1.82, 2.17)
$t_{1/2\alpha}$ (h)	5.03 (3.20, 7.89)	2.41 (1.62, 3.59)	2.09 (1.18, 3.68)

t_{1/2β} (h)	82.12 (71.39, 94.46)	33.77 (29.13, 39.15)	2.43 (2.02, 2.92)
CL (mL/h/kg)	3.19 (2.84, 3.59)	6.34 (5.64, 7.13)	0.50 (0.46, 0.55)
MRT (h)	98.60 (88.16, 110.29)	41.19 (35.98, 47.15)	2.39 (2.12, 2.71)
V_{ss} (mL/kg)	314.8 (277.8, 356.8)	261.1 (222.9, 305.9)	1.21 (1.06, 1.38)
Incremental Recovery (IU/dL per IU/kg)	0.92 (0.77, 1.10)	0.95 (0.81, 1.10)	0.97 (0.84, 1.12)
[†] PK parameters are presented in geometric mean (95% CI) Abbreviations: CI = confidence interval; C _{max} = maximum activity; AUC = area under the FIX activity time curve; t _{1/2α} = distribution half-life; t _{1/2β} = elimination half life; CL = clearance; MRT = mean residence time; V _{ss} = volume of distribution at steady state			

Pharmacokinetic Properties

In a Phase 3 study, 123 subjects received either 50 IU/kg or 100 IU/kg ALPROLIX. Pharmacokinetic assessments were conducted in 120 subjects. The estimated PK parameters were based on plasma FIX activity measured by one-stage activated partial thromboplastin time (aPTT) clotting assay. For ALPROLIX, the maximum activity concentration (C_{max}) was observed immediately following infusion, e.g., at 10 minutes from the start of the dosing. Following 50 IU/kg dose of ALPROLIX, the mean increase in circulating FIX activity from pre-infusion level was 0.98 IU/dL per IU/kg and the elimination half-life was 75 hours. As compared with 50 IU/kg following the 100 IU/kg ALPROLIX dose, the terminal plasma half-life increased by 25 hours and clearance decreased by 23%.

The ALPROLIX PK profile was comparable at Week 26 with the PK profile after the first dose. The PK parameters of ALPROLIX are summarized in Table 4.

Table 4: Pharmacokinetic Parameters (Arithmetic Mean, CV%) for rFIXFc activity data.

	rFIXFc	rFIXFc
PK Parameters	50 IU/kg (N = 93)	100 IU/kg (N = 27)
C _{max} (IU/dL)	47.6 (46%)	99.9 (20%)
AUC _{inf} (h*IU/dL)	1543.6 (26%)	3930.0 (19%)
CL (mL/kg/h)	3.46 (26%)	2.65 (22%)
V _{ss} (mL/kg)	311.1 (28%)	242.4 (25%)
Terminal T _{1/2} (h)	75.0 (34%)	100.7 (36%)

	rFIXFc	rFIXFc
PK Parameters	50 IU/kg (N = 93)	100 IU/kg (N = 27)
MRT (h)	91.8 (25%)	93.5 (25%)
IR (IU/dL per IU/kg)	0.982 (43%)	1.10 (22%)
Time to 1% FIX activity (d)	10.7 (20%)	15.8 (21%)
Time to 3% FIX activity (d)	5.85 (22%)	9.44 (20%)

Abbreviations: IR = incremental recovery; AUCinf = area under the FIX activity time curve; $T_{1/2}$ = elimination half-life; MRT = mean residence time; CL = bodyweight adjusted clearance; V_{ss} = bodyweight adjusted volume of distribution at steady-state, Time to 1% FIX activity = estimated time after dose when FIX activity has declined to approximately 1 IU/dL above baseline Time to 3% FIX activity = estimated time after dose when FIX activity has declined to approximately 3 IU/dL above baseline

Pediatric and Adolescent Pharmacokinetics

Pharmacokinetic (PK) parameters of ALPROLIX (rFIXFc) were determined for adolescents (12 to less than 18 years of age) in the phase 3 study, and for children (2 to < ~~less than~~ 12 years of age) in an open-label, multi-center study of pediatric previously treated patients. [see *Pediatric Use (8.4)*]

Pharmacokinetic parameters were evaluated following a 10-minute IV infusion in 11 evaluable adolescents who received a single dose of ALPROLIX. PK samples were collected pre-dose and at multiple time points up to 336 hours (14 days) post-dose. In a separate study, PK parameters were evaluated following a 10-minute IV infusion in 18 evaluable children (2 to < ~~less than~~ 12 years of age) who received a single dose of ALPROLIX. PK samples were collected pre-dose and at multiple time points up to 168 hours (7 days) post-dose. PK parameters for ALPROLIX were estimated based on the plasma FIX activity over time profile.

Table 5 presents the PK parameters calculated from the pediatric data of 29 subjects, 2 to < ~~less than~~ 18 years of age. Compared to adults, incremental recovery appeared to be lower and **bodyweight adjusted** clearance appeared to be higher in children less than 12 years of age. This may result in a need for **per kg bodyweight** dose adjustments in children less than 12 years of age. [see *Pediatric Use (8.4)*]

Comment: Table 5 parameter values need to be recalculated using arithmetic means

Table 5: Comparison of PK Parameters of rFIXFc by Age Category

PK Parameters ¹	Pediatric Study		Phase 3 Study
	<6 years (2, 4)	6 to <12 years (6, 10)	12 to <18 years (12, 17)
	N = 5	N = 13	N = 11
IR (IU/dL per IU/kg)	0.5927 (0.4945, 0.7103)	0.7175 (0.6122, 0.8409)	0.8470 (0.6767, 1.0600)
AUC/Dose (IU*h/dL per IU/kg)	22.94 (18.71, 28.11)	28.50 (24.43, 33.23)	29.50 (25.13, 34.63)
T_{1/2} (h)	63.61 (42.09, 96.14)	70.43 (61.05, 81.24)	82.22 (72.30, 93.50)
MRT (h)	79.00 (60.37, 103.38)	82.51 (72.72, 93.63)	93.46 (81.77, 106.81)
CL (mL/h/kg)	4.358 (3.559, 5.337)	3.509 (3.009, 4.091)	3.390 (2.888, 3.979)
V_{ss} (mL/kg)	344.4 (276.4, 429.2)	289.8 (237.5, 353.5)	316.8 (267.4, 375.5)

¹PK parameters are presented in **Arithmetic Geometric Mean (95% CI)**

Abbreviations: CI = confidence interval; IR = incremental recovery; AUC = area under the FIX activity time curve; T_{1/2} = elimination half-life; MRT = mean residence time; CL = **bodyweight adjusted** clearance; V_{ss} = **bodyweight adjusted** volume of distribution at steady-state

The PK evaluation of the adolescent subjects 12 to 17 years old showed that their PK profiles and the arithmetic means of PK parameters are similar to those of adults. Therefore, for subjects 12 years and older, an age-based dose adjustment is not required.

Comment: the complete subsection “Population Pharmacokinetics” should be deleted and not replaced, because it does not add clinically relevant information for the prescribing and treating physician.

Population Pharmacokinetics

A population PK model was developed based on PK data from 12 subjects in a phase 1/2a study and 123 subjects in a phase 3 study. The subjects were 12 to 76 years old and weighed between 45 kg and 186.7 kg. The population estimate for the typical CL of rFIXFe is 2.39 dL/h, typical volume of central compartment (V1) is 71.4 dL and V_{ss} is 198.3 dL. The model was used to predict the activity time profile following dosing with ALPROLIX in patients with severe hemophilia B [see Table 6].

Table 6: Predicted Factor IX Activity Following a Single Dose of ALPROLIX[†]

Dose (IU/kg)	End of Infusion	12 hours	24 hours (Day 1)	36 hours	48 hours (Day 2)	72 hours (Day 3)	Day 5	Day 7	Day 10	Day 14
	Median [5 th , 95 th]									
50	50.8	21.1	14.8	10.9	8.51	5.57	3.07	1.93	1.10	0.559
	[30.4, 84.5]	[13.5, 33.6]	[9.78, 22.7]	[6.79, 17.1]	[5.14, 13.2]	[3.05, 9.27]	[1.44, 5.62]	[0.795, 3.71]	[0.277, 2.33]	[0, 1.38]
100	102	42.3	29.5	21.8	17.0	11.1	6.14	3.88	2.19	1.08
	[60.8, 169]	[26.8, 67.3]	[19.6, 45.5]	[13.7, 34.1]	[10.5, 26.6]	[6.22, 18.5]	[3.05, 11.0]	[1.82, 7.28]	[0.775, 4.56]	[0.125, 2.58]

[†]see Dosage and Administration (2)

Measured factor IX activity in 14 subjects undergoing surgical procedures in a clinical study was consistent with the values predicted by the population PK model. A sample perioperative dosing regimen to achieve target factor IX levels, as simulated by this model, is shown in Table 7.

Table 7: Predicted Factor IX Activity for a Sample Perioperative Dosing Regimen[†]

Day at Dose ²	Time at Dose (hr)	Dose (IU/kg)	Trough ³ (IU/dL) Median [5 th , 95 th]
0	0	100	NA
0	8	80	47.3 [30.7, 73.5]
1	24	80	58.5 [38.6, 89.2]
2	48	80	55.3 [36.4, 85.1]
3	72	80	57.5 [38.0, 88.6]
5	120	70	39.8 [25.0, 66.4]
7	168	70	33.5 [20.6, 55.4]
9	216	70	31.0 [18.9, 50.4]
11	264	70	29.7 [18.6, 50.0]

Day at Dose²	Time at Dose (hr)	Dose (IU/kg)	Trough³ (IU/dL) Median {5th, 95th}
13	312	70	29.3 [17.2, 47.8]

¹See *Dosage and Administration* (2)

²Day 0 – day of surgery

³Target Factor IX trough activity levels per WFH 2008 and WFH 2012

CLINICAL PHARMACOLOGY RECOMMENDATION

- The results of the PK analyses and conclusions are acceptable and the proposed regimens for rFIXFc given to adults and adolescents older than 12 years appear to be adequate to achieve and, in prophylactic regimens, sustain therapeutic concentrations (50 IU/kg once weekly, 100 IU/kg every 10 days).
- Pediatric patients younger than 12 years may be in need for a “per kg bodyweight” dose adjustments.

Carl-Michael Staschen, M.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Iftexhar Mahmood, Ph.D.
Clinical Pharmacology Reviewer
Division of Hematology
Office of Blood Review & Research

Basil Golding, M.D.
Division Director, Division of Hematology
Office of Blood Review & Research

1. Study Title: A Phase I/IIa safety and pharmacokinetic study of intravenous rFIXFc in previously treated hemophilia B patients. Study Number: SYN-FIXFc-07-001

Objectives:

Primary Objective: The primary objective of the study was to assess safety of rFIXFc at doses ranging from 1 to 100 IU/kg.

Secondary Objective: The secondary objective of the study was to estimate the PK parameters of rFIXFc at doses ranging from 12.5 to 100 IU/kg.

Study Design

This was a Phase I/IIa open-label, multi-center, safety, dose-escalation study designed to evaluate the safety and PK of a single dose of rFIXFc (liquid drug product) given as an IV infusion over approximately 10 minutes in previously treated adult patients, diagnosed with severe hemophilia B. Six dose levels, 1, 5, 12.5, 25, 50, and 100 IU/kg were planned for evaluation in the study. Male adult patients were sequentially enrolled at 7 different sites. Fourteen (14) patients received an IV infusion of rFIXFc. One patient each received a dose of 1, 5, 12.5, and 25 IU/kg; 5 patients each received 50 IU/kg and 100 IU/kg. All patients enrolled and treated with rFIXFc in the study were followed for 30 days after administration of FIXFc for safety and PK assessments for those patients receiving rFIXFc at dose levels 12.5 to 100 IU/kg.

Methods of Analysis

Blood samples were to be analyzed at central laboratories for

- FIX activity using an aPTT-based assay. Pharmacokinetics based on rFIXFc activity measurements were performed on the baseline subtracted FIX activity versus time data
- rFIXFc concentrations antigen performed by a validated -(b)(4)-.

All patients enrolled in the study and who received any amount of rFIXFc were included in the evaluation for immunogenicity (antibody development).

A validated one-stage activated partial thromboplastin time (aPTT) clotting assay was employed to measure FIX activity. PK parameters were calculated using an open 2-compartment model (software -----(b)(4)-----)

Results:

a. FIXFc Activity Pharmacokinetics

PK results are presented in Table 1. The decline of FIX activity exhibited biexponential disposition following a short intravenous infusion. The terminal $T_{1/2-\beta}$, CL, Vss, and MRT appeared to be dose-independent over the dose range from 25 IU/kg to 100 IU/kg. An apparent dose-dependent, linear increase in FIX activity was observed on Cmax and on AUCinf. In addition, the incremental recovery IR (CV%) was calculated for all doses.

Table 1: rFIXFc activity pharmacokinetic parameters (Mean, CV-%) in hemophilia B patients

PK-Parameter	IV-Dose (IU/kg)		
	25 (N=1)	50 (N=5)	100 (N=5)
C _{max} (IU/dL)	20.4	47.5 (27%)	98.5 (8%)
AUC _{inf} (h·IU/dL)	766	1,700 (32%)	4020 (25%)
T _{1/2-α} (h)	0.612	3.31 (95%)	10.3 (55%)
T _{1/2-β} (h)	53.5	57.6 (14%)	56.5 (25%)
CL (mL/kg/h)	3.56	3.44 (24%)	2.84 (23%)
V _{ss} (mL/kg)	271	262 (21%)	183 (15%)
MRT (h)	76.2	77.0 (9%)	65.9 (16%)
IR (IU/dL per IU/kg)	0.771	0.87 (25%)	1.02 (11%)

C_{max} = maximum activity, IR = incremental recovery

b. rFIXFc Antigen Pharmacokinetics

rFIXFc plasma concentrations declined in a biexponential fashion following the short IV infusion. The primary PK parameter values for CL, V_{ss} and MRT appear to be dose-independent, although this assessment is limited by single patient data at the 25 IU/kg dose level. A dose-dependent, linear increase in systemic rFIXFc plasma exposure was observed for C_{max} and for AUC. No neutralizing or binding antibodies to rFIXFc were detected in any patient.

Pharmacokinetic Conclusions

Apparent dose-proportional increases in C_{max} and AUC_{inf} were observed for both rFIXFc antigen and activity following the administration of doses of 25 through 100 IU/kg, while the V_{ss} and Cl were approximately similar across all doses. These results indicate that rFIXFc antigen and activity exhibited apparent linear PK over the therapeutic dose range evaluated, and that the test product had a limited distribution volume.

Reviewer's Comments:

- The results of the PK analysis and Applicant's conclusions are acceptable from a Clinical Pharmacology perspective.

2. Study Title: An open-label, multi-center evaluation of the safety, pharmacokinetics, and efficacy of recombinant, long-acting coagulation factor IX Fc fusion protein (rFIXFc) in the prevention and treatment of bleeding in previously treated subjects with severe hemophilia B (Study Number: 998HB102)

Study Design

Study 998HB102 was an open-label, multicenter study that was designed to evaluate safety specifically with respect

- to the incidence of inhibitor formation,
- to confirm the PK findings from the Phase 1/2a study, and
- to determine the clinical efficacy of rFIXFc (lyophilized drug product) in the
 - control and prevention of bleeding
 - routine prophylaxis
 - perioperative management.

In Study 998HB102, PK data were collected in all subjects. BeneFIX® was selected as the comparator for PK profiling.

Drug rFIXFc description

rFIXFc was supplied in a kit that contained several components: a vial of lyophilized drug, the diluent syringe, a ---(b)(4)-- filter device, and a -----(b)(4)----- . The lyophilized powder was in a clear glass vial containing 500, 1000, or 3000 IU of rFIXFc (nominal strengths).

BeneFIX description

BeneFIX was to be prepared and administered following the manufacturer's prescribing information. The subjects enrolled in the Sequential PK subgroup of Arm 1 were to receive a single dose of BeneFIX (50 IU/kg IV) over 10 minutes in the clinic as the first study dose.

Assay Methodology

The plasma FIX activity was measured by a one-stage (aPTT) clotting assay and verified for use in the PK analysis. The assay was validated for rFIXFc, BeneFIX and human FIX in human plasma samples to a lower limit of quantitation of -(b)(4)- of FIX.

Treatments

All subjects (≥ 12 y) were to receive study treatment according to the assigned treatment group:

Arm 1, Weekly Prophylaxis

- 50 IU/kg rFIXFc once every 7 days initially, then at a dose indicated by the subject's baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher
- Sequential PK subgroup, at selected sites, for PK profiling:

- Single dose of 50 IU/kg BeneFIX at baseline prior to first dose of rFIXFc
- Single dose of 50 IU/kg rFIXFc, a minimum of 120 hours following BeneFIX dose
- Single dose of 50 IU/kg rFIXFc at Week 26

Arm 2, Individualized Interval Prophylaxis

- 100 IU/kg rFIXFc once every 10 days initially, then at an interval derived from the baseline PK assessment that ensured a target trough of 1% to 3% above baseline or higher

Arm 3, Episodic Regimen

- 20 to 100 IU/kg rFIXFc, or the dose indicated by the subjects' baseline PK to target a plasma level of 20% to 100%, as needed for the treatment of mild to severe bleeding episodes

Arm 4, Perioperative Management

- 40 to 100 IU/kg rFIXFc, as needed for the surgical prophylaxis (perioperative management) and treatment of bleeding episodes

For study 98HB102, the PK samples were collected according to the schedule in Table 1.

Table 1: Phase 3 Study: rFIXFc PK Sampling Schemes

Study Arm/Subgroup	Sample Times
Arm 1/Sequential PK	Pre-dose; 10 minutes, 1, 3, 6, 24, 48, 96, 144, 168, 192, and 240 hours post-dose
Arm 1/Non-Sequential PK	Pre-dose; 10 minutes, 3, 24, 48, 96, 168, and 240 hours post-dose
Arm 2	Pre-dose; 10 minutes, 3, 24, 48, 96, 168, 240, 288, and 336 hours post-dose
Arms 3 and 4	Pre-dose; 10 minutes, 3, 24, 48, 96, and 168 hours post-dose

Arm1/Sequential PK BeneFIX (50 IU/kg IV) PK sampling times: pre-dose, 10 minutes, 1, 3, 6, 24, 48, 72, and 96 hours post-dose

Prior to the first dose of rFIXFc or BeneFIX (for subjects in the Sequential PK subgroup of Arm 1), all subjects were to undergo a 120-hour washout of FIX-containing products.

Pharmacokinetic Analyses

The PK profiles of rFIXFc were adequately described by a 2-compartmental model and the estimated PK parameters for rFIXFc are summarized in Table 2. The maximum concentration (C_{max}) was observed immediately following infusion, e.g., at 10 minutes from the start of the dosing. Following the 50 IU/kg dose, the mean increase in circulating FIX activity from pre-infusion level was 0.98 IU/dL per IU/kg and the terminal elimination half-life (T_{1/2-β}) was 75 hours. Following the 100 IU/kg dose, the mean increase in circulating FIX activity from pre-infusion level was 1.1 IU/dL per IU/kg and T_{1/2-β} was 100.7 hours. The PK profile of rFIXFc was stable over 26 weeks, with the time course of activity predictable from the first dose.

Table 2: Estimated pharmacokinetic parameters (Mean, CV%) in patients with hemophilia B.

Dose	50 IU/kg (N = 93)	100 IU/kg (N = 27)
PK Parameters	rFIXFc	rFIXFc
C _{max} (IU/dL)	47.6 (46%)	99.9 (20%)
AUC _{inf} (d*IU/dL)	25.7 (26%)	65.5 (19%)
CL (mL/kg/h)	3.46 (26%)	2.65 (22%)
V _{ss} (mL/kg)	311.1 (28%)	242.4 (25%)
T _{1/2-β} (h)	75.0 (34%)	100.7 (36%)
MRT (h)	91.8 (25%)	93.5 (25%)
IR (IU/dL per IU/kg)	0.98 (43%)	1.10 (22%)
Time to 1% FIX activity (d)	10.7 (20%)	15.8 (21%)
Time to 3% FIX activity (d)	5.85 (22%)	9.44 (20%)

- Results for 50 IU/kg calculated after pooling 4 subgroups

- Time to 1% FIX activity = estimated time after dose when FIX activity has declined to approximately 1 IU/dL above baseline

- Time to 3% FIX activity = estimated time after dose when FIX activity has declined to approximately 3 IU/dL above baseline

The PK profiles of plasma FIX activity for rFIXFc and BeneFIX were adequately described by a 2-compartmental model. rFIXFc showed a 2.43-fold increase in terminal T_{1/2-β} compared with BeneFIX, with a corresponding 2.21-fold extension of time to 1% above baseline.

Pediatric Pharmacokinetic Results

The PK evaluation of 11 adolescent subjects 12 to 17 years old showed that their PK profiles and the arithmetic means of PK parameters (Table 3) are similar to those of adults in the Sequential PK subgroup. The Sequential PK subgroup was designed to characterize the PK of rFIXFc and included no adolescent subjects. Furthermore, the population PK analysis did not find age to have any statistically significant impact on the PK variability of rFIXFc. Thus, the results indicate that for subjects 12 years of age or older, there is no requirement for age-based dose adjustment.

Table 3: Comparison of PK parameters in adolescent (12–17 years old) and adult subjects

	K IU/dL per IU/kg	DNAUC IU·h/dL per IU/kg	t _{1/2β} hours	MRT hours	CL mL/h/kg	V _{ss} mL/kg
Adolescents N=11	0.893 ± 0.325	30.6 ± 7.08	94.3 ± 40.3	100 ± 28.2	3.46 ± 0.943	337 ± 91.6
Adults ^a N=22	1.015 ± 0.5965	32.3 ± 8.35	86.5 ± 32.17	102 ± 30.2	3.30 ± 0.937	327 ± 92.1

^a Sequential PK subgroup after first dose.

Note: All values are arithmetic mean ± SD.

Abbreviations: K = incremental recovery, DNAUC = dose normalized area under the plasma activity time curve,

t_{1/2β} = elimination half-life, MRT = mean residence time, CL = clearance, V_{ss} = volume of distribution at steady-state

Binding and Neutralizing Antibodies

No subject developed detectable neutralizing antibody (inhibitor) to FIX (≥ 0.6 BU).

Four subjects had low positive anti-rFIXFc drug antibody (ADA) responses, of which 3 exhibited an ADA response at Screening or Baseline but reverted to negative during the study (Subjects -----(b)(6)-----). One subject (Subject --(b)(6)--, Arm 2) had borderline negative values for ADA at screening and baseline as well as at Weeks 4, 16, 26, and 39, and had a borderline positive result at the end of study (Day 338). None of the 4 ADA positive subjects had a clinically significant change in estimated PK parameters.

Pharmacokinetic Conclusions

- The mean elimination half-life ($T_{1/2-\beta}$) of rFIXFc was 75.0 hours after a dose of 50 IU/kg and 100.7 hours after 100 IU/kg.
- The incremental recovery of rFIXFc was close to 1 IU/dL per IU/kg, suggesting that no additional dose adjustment based on recovery is required.
- The PK profile of rFIXFc was stable over 26 weeks.
- The PK profiles and estimated parameters of adolescents were similar to adults
- Compared to BeneFIX, rFIXFc has a 2.43-fold relative increase in $T_{1/2-\beta}$.
- No clinically significant impact of ADA detection in 4 subjects on PK

Reviewer's Comments:

- The results of the PK analysis and Sponsor's conclusions are acceptable from a Clinical Pharmacology perspective.

3. Study Title: A population pharmacokinetic analysis of rFIXFc in patients with severe hemophilia B. **Report Number:** -----(b)(4)-----

Objectives

- Characterize the population pharmacokinetics of rFIXFc in severe hemophilia B patients and estimate population PK parameters of rFIXFc;
- Identify demographic and clinical factors (covariates) that are potential determinants of rFIXFc PK variability in hemophilia B patient population;
- Evaluate dosing regimens using population PK model-based simulation for routine prophylaxis, control and prevention of bleeding episodes, and peri-operative management.

Data Sources

Study SYN-FIXFc-07-001

Study SYN-FIXFc-07-001 was a Phase 1/2a open label, multi-center, safety, dose escalation study designed to evaluate the safety and PK of a single dose of rFIXFc given as an intravenous (IV) infusion over approximately 10 minutes to 14 previously treated adult patients, diagnosed with severe hemophilia B. Patients receiving rFIXFc at ascending dose levels of 12.5 to 100 IU/kg underwent PK sampling pre- and post-dose of FIXFc at the designated collection times: the end of the infusion, 15 minutes, 1 hour to 336 hours after the end of infusion.

Study 998HB102

Study 998HB102 was an open-label multi-center study to evaluate the safety, tolerability, PK, and efficacy of rFIXFc in subjects with severe hemophilia B (defined as ≤ 2 IU/dL [$\leq 2\%$] endogenous FIX). 123 subjects at 50 investigational sites in 17 countries were enrolled into 1 of the following treatment arms: fixed weekly interval regimen (Arm 1), individualized interval regimen (Arm 2), episodic treatment (Arm 3), or surgery (Arm 4). PK samples were collected at pre-dose, 10 min, 1 hour to 336 hours post-dose

Table 1 lists the summary of final input for the modeling dataset.

Table 1: Summary of final input for the modeling dataset

Study	No. of Patients	No. of FIX Activity records	No. of Doses
Phase 1/2a (SYN-FIXFc-07-001)	12	156	12
Phase 3 (998HB102)	123	1244	1310

Drug Products and Bioanalytical Methods

For the Phase 1/2a Study SYN-FIXFc-07-001, the drug product was formulated as ----(b)(4)----.

The formulation in the Phase 3 study was given as lyophilized powder.

PK samples collected from all subjects were determined using a one-stage activated partial thromboplastin time (aPTT) clotting assay. The population PK modeling was performed using measured FIX activity data.

Modeling Software

------(b)(4)----- was used for the population PK model development.

Results

Model Building

Development of the Base Model

A 3 compartment model was chosen as the base model. Inclusion of additional inter-individual variability (IIV) terms on other PK parameters was tested sequentially. Inclusion of IIV terms was found to provide a significant reduction in the OFV for all six PK parameters. However, inclusion of IIV on Q3 was associated with a high standard error (87%), indicating that it cannot be estimated with precision, Model 10, containing ETA on CL/V1/Q2/V2/V3, and covariance term between CL and V1, was therefore chosen to continue with further evaluation. Goodness-of-fit plots show that the data were described reasonably well. BW was entered as allometric covariate on CL and on V1

Final Model

Model 17IOV was the final model and evaluations were conducted with Model 17IOV. Table 2 lists population PK parameter estimates, IIV and inter-occasion variability (IOV), as well as residual errors, which were all estimated with reasonable precision. Figure 1 provides goodness-of-fit plots.

Model Qualification

The non-parametric bootstrap results indicated that the final model 17IOV was stable. The results of the Visual Predictive Check (VPC) indicated that the final model was able to reproduce both the central tendency and variability of the observed data on the time scale.

External Validation with the Trough/peak Activity Dataset

The predictive capability of the final model was further examined using an external validation dataset which included all the trough/peak activity records. No model estimation was performed. Individual predictions were plotted against observations in Figure 3. Plots showed good correlation between predicted and observed data ($R^2=0.9857$, $P<0.001$).

Table 2: Summary of rFIXFc Population PK Model 17IOV

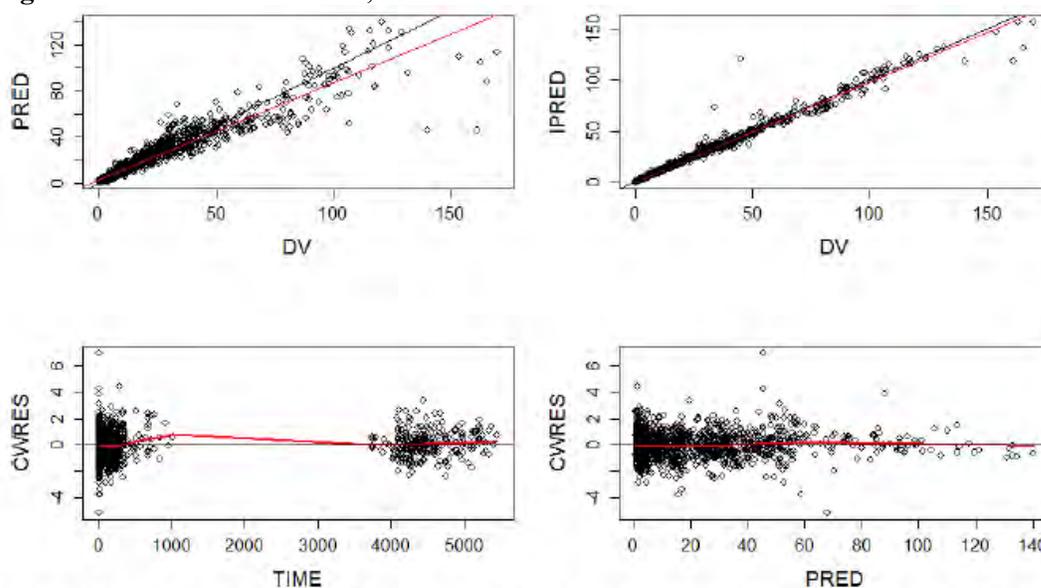
Parameter	Population Estimate	95% CI ^a of Population Estimate	IIV ^b (%)	IIV OMEGA, % RSE ^c	IOV (%)	IOV OMEGA, % RSE
$CL = \theta 1 \times \left(\frac{\text{Body Weight}}{73}\right)^{0.436}$						
Typical CL $\theta 1$ (dL/h for 73 kg subject)	2.39	2.27 – 2.51	17.7	22.2	15.1	36.1
BW exponent on CL	0.436	0.230 - 0.642				
$V1 = \theta 2 \times \left(\frac{\text{Body Weight}}{73}\right)^{0.396}$						
Typical V1 $\theta 2$ (dL for 73 kg subject)	71.4	65.1 – 77.7	21.7	45.1	17.4	59.1
BW exponent on V1	0.396	0.116 – 0.676				
Q2 (dL/h)	1.67	1.48 – 1.86	35.8	26.4	--	--
V2 (dL)	87.0	75.9 – 98.1	46.2	21.0	--	--
Q3 (dL/h)	39.3	31.3 – 47.3	--	--	--	--
V3 (dL)	39.9	34.3 – 45.5	37.7	29.9	--	--
Correlation between CL and V1			75.6	28.9	--	--
Residual Error: Proportional 10.6% Additive 0.24 IU/dL						

^a95% CI: 95% confidence interval. The lower and upper limits for 95% CI were calculated asymptotically using the standard errors estimated by the covariance step in ^b(4)

^bIIV: Inter-individual variability, calculated as $(\text{variance})^{1/2} \times 100\%$.

^c%RSE= relative standard error of the IIV variance, calculated as $[(\text{standard error of variance}) \times 100\%]/(\text{variance})$

Figure 1: Goodness-of-fit Plots, Model 17IOV



Note: black line is the unit line; red line represents the linear regression line in the upper panels and the LOESS smoother in the lower panels; DV: Observed FIX activity (IU/dL); PRED: prediction by population PK parameter estimates, unit is IU/dL; IPRED: prediction by individual PK parameter estimates, unit is IU/dL; CWRES: conditional weighted residual; TIME, unit is hour.

Dosing regimen simulations

The population PK model was used to simulate the FIX activity time profiles following single doses of 50 and 100 IU/kg for control of bleeding, or at steady-state following a prophylactic dosing regimen of either 50 IU/kg once weekly, or 100 IU/kg once every 10 or 14 days in 1000 subjects.

- The simulations of weekly dosing of 50 IU/kg of rFIXFc predicted that more than 95% of the population has trough/peak within target range i.e. trough \geq 1% and peak $<$ 150%.
- Simulations of 100 IU/kg of rFIXFc every 10 days predicted that more than 85% of the population was within the range of 1% to 150%.
- Simulations of 100 IU/kg of rFIXFc every 14 days predicted more than 50% of the population within the range of 1% to 150%.
- Simulation of dosing regimens for peri-operative management indicated that the surgical procedures did not alter the PK properties of rFIXFc.

Reviewer's Comments:

- In general, the objectives have been met and the results of the population PK analysis and simulations are acceptable from a Clinical Pharmacology perspective.
- In Section 8.1.2: Development of the Base Model and Assessment of Inter-individual Variability (IIV) (p.30/31) it is stated: "However, inclusion of IIV on Q3 was associated with a high standard error (87%), indicating that it cannot be estimated with precision, Model 10 instead of 11, containing ETA on CL/V1/Q2/V2/V3, and covariance term between CL and V1, was therefore chosen to continue with further evaluation." Note, all structural parameters in the PopPK model should be estimated together with all their respective between-subject-variabilities (BSV). It is not acceptable to subjectively exclude a BSV estimate because the respective residual standard error (%RSE) is considered "too high". Omitting random variability of a population parameter estimate would lead in subsequent stochastic simulations to biased and optimistic statistical confidence intervals, rendering the predictions less informative.
- In the population PK study simulations for prophylaxis predicted that at a dose of 100 IU/kg of rFIXFc every 10 days more than 85% of the population was within the range of 1% to 150%. However, simulations of 100 IU/kg of rFIXFc every 14 days predicted more than 50% of the population within the range of 1% to 150%. These results suggest that a dosing regimen of 100 IU/kg every 14 days nearly 50% of the patients will not achieve therapeutic concentrations. To achieve and sustain therapeutic concentrations in the majority of patients a dosing frequency of every 10 days appear to be sufficient.

4. Study Title (Study is ongoing):

An open-label, multicenter evaluation of safety, pharmacokinetics, and efficacy of recombinant coagulation factor IX Fc fusion protein, --(b)(4)--, in the prevention and treatment of bleeding episodes in pediatric subjects with hemophilia B. (**Study Number:** 9HB02PED)

Study Design

The ongoing pediatric study (9HB02PED) is an open-label, multicenter evaluation of the safety, PK, and efficacy of rFIXFc for routine prophylaxis in pediatric PTPs with severe hemophilia B (defined as ≤ 2 international units [IU]/dL [2%] endogenous FIX or a documented genotype known to produce severe hemophilia). Subjects are to be younger than 12 years of age at enrollment and have at least 50 exposure days (EDs) to FIX products prior to enrollment. The duration of study participation for each subject is approximately 54 weeks, including treatment with rFIXFc for approximately 50 weeks to obtain at least 50 EDs and a follow-up period. After completing the PK assessment, subjects begin a weekly prophylactic treatment with an initial weekly dose of 50 to 60 IU/kg.

Eighteen subjects (5 subjects <6 years of age and 13 subjects 6 to <12 years of age) had evaluable rFIXFc PK profiles and are included in the pharmacokinetic analysis set.

At the Baseline Visit (28 days prior to Day 1) subjects received a single intravenous (IV) injection of prestudy FIX (blood sample time points: 0, 0.5, 3, 10, 24, and 48 h) and on Day 1 received a single IV injection of rFIXFc (blood sample time points: 0, 0.5, 3, 10, 24, 72, 120, and 168 h). Both drugs were administered in the clinic under medical supervision at a nominal dose of 50 IU/kg given over 10 minutes.

Bioanalytical Methods and Software

The estimated PK parameters were based on plasma FIX activity measured by a validated one-stage activated partial thromboplastin time (aPTT) clotting assay.

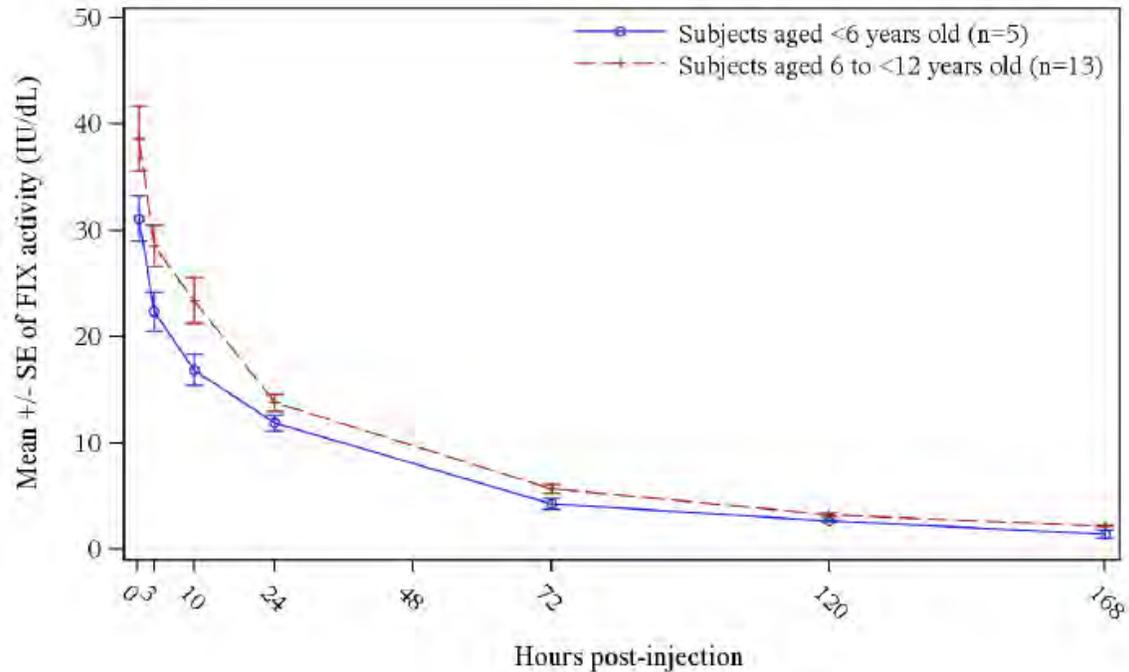
The FIX activity-over-time profiles, corrected by baseline and residual drug, were analyzed by noncompartmental analysis (NCA) using -----(b)(4)-----.

Results

FIX activity increased immediately following IV injection of rFIXFc at 50 IU/kg in each age cohort. After the end of the injection, the decline of FIX activity exhibited multiexponential decay characteristics (Figure 1).

The relevant PK parameter estimates derived from noncompartmental analysis of aPTT activity data are compared to PK results from the Phase 3 study and shown in Table 1a.

Figure 1: Mean FIX activity over time after 50 IU/kg of rFIXFc.



Data presented are observed FIX activity without subtraction of endogenous baseline FIX level and residue FIX level from the previous treatment prior to the PK dose.

Table 1a: Comparison of PK parameters of rFIXFc by age category: arithmetic mean (95% CI)

	Pediatric Study (9HB02PED)		Phase 3 Study (998HB102)	
	<6 years (N = 5)	6 to <12 years (N = 13)	12 to 17 years (N = 11)	≥18 years (N = 109)
IR (IU/dL per IU/kg)	0.5980 (0.4814, 0.7146)	0.7422 (0.6114, 0.8731)	0.8929 (0.6744, 1.1114)	1.0199 (0.9449, 1.0950)
DNAUC (IU·h/dL per IU/kg)	23.18 (18.59, 27.77)	29.38 (24.65, 34.10)	30.23 (25.73, 34.73)	33.44 (31.85, 35.02)
t_{1/2} (h)	66.40 (39.95, 92.85)	72.23 (62.14, 82.32)	83.59 (72.89, 94.30)	78.41 (74.99, 81.84)
MRT (h)	80.52 (58.18, 102.86)	84.06 (74.59, 93.53)	95.13 (82.70, 107.55)	90.37 (86.64, 94.10)
CL (mL/h/kg)	4.406 (3.486, 5.326)	3.613 (3.065, 4.161)	3.483 (2.885, 4.081)	3.178 (3.026, 3.329)
V_{ss} (mL/kg)	349.0 (266.0, 432.0)	303.0 (250.8, 355.2)	326.0 (271.5, 380.5)	282.5 (267.9, 297.1)

CI = confidence interval; CL = clearance; DNAUC = dose-normalized area under the curve; IR = incremental recovery; MRT = mean residence time; PK = pharmacokinetics; rFIXFc = recombinant coagulation factor IX Fc fusion protein; t_{1/2} = terminal half-life; V_{ss} = volume of distribution at steady state.

Some trends in the results were noted. Specifically, a decrease in the mean IR and dose-normalized area under the curve (DNAUC) and an increase in mean body weight-normalized CL for pediatric subjects <12 years of age, compared to the adult (≥ 18 years) values, are evident (Table 1b). However, a fair comparison has to take into account the relatively low numbers of pediatric subjects in respective age groups. Trends in $T_{1/2}$ and MRT estimates were less pronounced.

Table 1b: Mean relative change (%) of relevant PK parameters grouped by age category (referenced to adult values = 100%)

PK Parameter	Pediatric Study (9HB02PED)		Phase 3 Study (998HB102)	
	2 to < 6 years (N=5)	6 to < 12 years (N=13)	12 – 17 years (N=11)	≥ 18 years (N=109)
IR (IU/dL per IU/kg)	-41 %	-27 %	-13 %	100 %
DNAUC (IU·h/dL per IU/kg)	-31 %	-12 %	-10 %	100 %
CL (mL/h/kg)	+39 %	+14 %	+10 %	100 %

IR = incremental recovery, DNAUC = dose normalized area under the curve, CL = Clearance

Despite the observed trends in the PK parameters between pediatric subjects <12 years of age in comparison to adults, the relative PK behavior of rFIXFc with respect to prestudy FIX was preserved across all age groups. In the Phase 3 study, rFIXFc showed a 2.42-fold increase in $T_{1/2}$ in comparison to comparator BeneFIX. In the pediatric study, in which a variety of prestudy FIX treatments were evaluated, the ratio of $T_{1/2}$ for rFIXFc versus prestudy treatment ranged from 2.91 to 7.89 (2.91 to 5.04 in subjects receiving BeneFIX as prestudy FIX).

Analyzing the pediatric FIX PK data obtained to date and comparing results to PK data obtained in adult and adolescent subjects, the following conclusions can be drawn:

- Compared to adults, there is a substantial decrease in mean incremental recovery (IR) (-41%) and an increase in mean bodyweight adjusted CL (+39%) in pediatric patients 2 to < 6 years of age. These differences should be taken into account when dosing children 2 to < 6 years of age.
- Consistent across age groups, rFIXFc is observed to have a prolonged $T_{1/2}$ and reduced CL compared with other FIX products.

Reviewer’s Comments:

- In general, the results of the interim pediatric PK analysis and conclusions are acceptable from a Clinical Pharmacology perspective.
- A final assessment, however, can only be made after submission of the final study report