

CLINICAL PHARMACOLOGY REVIEW

Division of Hematology
Office of Blood Review & Research

STN 125385/0

Product: Factor XIII Concentrate (Human)

Sponsor: CSL Behring GMBH

Indication: For routine prophylactic treatment of Factor XIII deficiency

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Reviewer: Iftekhar Mahmood, Ph. D.

RPM: Nannette Cagungun

Through: Basil Golding, M.D.

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INTRODUCTION

Congenital deficiency of Factor XIII is an extremely rare hereditary disorder associated with potentially life-threatening bleeding. The estimated incidence is approximately 1 in 2 million with a high prevalence of consanguinity within affected families. Congenital Factor XIII deficiency is the bleeding disorder with the highest risk of potentially life-threatening intracranial hemorrhage, and about 25 to 60% of the affected patients experience an intra-cranial hemorrhage at least once during their lifetime. Intracranial hemorrhage is responsible for 80% of all deaths in this population. There is a very high rate of recurrence in patients who do not receive appropriate prophylaxis. The life-threatening consequences of Factor XIII deficiency require prophylactic administration of Factor XIII as soon as the diagnosis is established, usually in infancy or early childhood. Factor XIII supplementation has been achieved by administration of whole blood, fresh frozen plasma, cryoprecipitate, or heat-treated Factor XIII Concentrate (Human) from human plasma.

Factor XIII is a plasma pro-enzyme composed of 4 proteins: 2 A subunits and 2 B subunits; it promotes cross-linking of fibrin during blood coagulation. Factor XIII is converted by calcium

and thrombin into the active enzyme Factor XIIIa, which covalently links fibrin molecules to each other and other molecules to fibrin. It converts the loose fibrin polymer into a firm, highly organized, cross-linked structure with increased tensile strength, firmly anchored to the site of the wound and possessing an in-built resistance to fibrinolysis.

Investigational recombinant Factor XIII products are composed of only the A subunits (homodimer) and not the carrier B subunits. However, the B subunit appears to stabilize the structure of the A subunit and to protect it from proteolysis. Free Factor XIII in plasma that is not attached to the B subunit undergoes slow spontaneous activation without cleavage of the activation peptide and free binding sites on B are essential for retention of injected A subunits in plasma. This structure-function relationship of the Factor XIII molecule has implications for the levels of protein and for initiation of and dosing levels in prophylaxis. In 17% of patients, for example, the abnormality is in the B subunit, and in these patients, survival of the Factor XIII molecule will be shorter.

Factor XIII Concentrate (Human) is a purified, heat-treated, Factor XIII Concentrate derived from human plasma. It is approved in parts of Europe and other regions of the world as Fibrogammin P, and CSLB is presently the only manufacturer of this product.----(b)(4)-----

----- (b)(4) -----

---. CSLB is seeking marketing approval for the indication of routine prophylactic treatment of Factor XIII deficiency. The studies reported in this review were conducted as part of the clinical development program with the purpose of determining the pharmacokinetics (PK) of Factor XIII Concentrate (Human).

CLINICAL PHARMACOLOGY LABELING COMMENTS

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12.1 Mechanism of Action

[Trade Name] (Factor XIII) is an endogenous plasma glycoprotein consisting of two A-subunits and two B-subunits. Factor XIII circulates in blood plasma and is present in platelets, monocytes, and macrophages. Factor XIII appears in 2 forms, a heterotetrameric (A₂B₂) plasma protein with a molecular weight of about 320 kilodaltons and a homodimeric (A₂) cellular form. Factor XIII is a proenzyme that is activated, in the presence of calcium ions, by thrombin cleavage of the A-subunit to become activated factor XIII (factor XIIIa). Intracellularly, the homodimeric form (A₂) of only the A-subunits is found. The B-subunits in plasma have no enzymatic activity.

The B-subunits function as carrier molecules for the A-subunits, stabilize the structure of the A-subunits and protect them from proteolysis. The structure-function relationship of the factor XIII molecule has implications for levels of circulating protein and for initiation of, and dosing levels in prophylaxis. In 17% of patients, for example, the abnormality is in the B subunit, and in these patients, survival of the factor XIII molecule will be shorter.³ Factor XIII investigational products differ in composition and may not contain both A-subunits and B-subunits. Free binding sites on B-subunits are essential for retention of injected A subunits in plasma.⁴

Factor XIII has important functions in hemostasis and wound healing. Factor XIIIa promotes cross-linking of fibrin during coagulation and is essential to the physiological protection of the clot against fibrinolysis. Factor XIIIa is a transglutaminase enzyme that catalyzes the cross-linking of fibrin α - and γ -chains for fibrin stabilization and renders the fibrin clot more elastic and resistant to fibrinolysis.^{5,6} Factor XIIIa also cross-links α_2 -plasmin inhibitor to the α -chain of fibrin, resulting in protection of the fibrin clot from degradation by plasmin. Cross-linked fibrin is the end result of the coagulation cascade, and provides tensile strength to a primary hemostatic platelet plug.⁶

12.2 Pharmacodynamics

In clinical studies, the intravenous administration of [Trade Name] demonstrated an immediate increase in plasma levels of Factor XIII lasting approximately 28 days. In the pharmacokinetic study, after the third 40 IU/kg dose (steady state), the mean increase in FXIII activity levels was 83% with a range of 48 to 114% over the baseline (~~see [Pharmacokinetics \[12.3\]](#)~~).

12.3 Pharmacokinetics

A 12-week prospective, open-label, ~~uncontrolled~~, multicenter pharmacokinetic ~~and safety~~ study was conducted in 7 females and 6 males with congenital FXIII deficiency, ranging in age from 5 to 42 (3 children, 2 adolescents, 8 adults).

Each subject received 40 IU/kg [Trade Name] intravenously every 28 days for a total of three doses administered at approximately 250 IU/min. Blood samples for doses 1 and 2 were drawn from patients to determine the FXIII activity level at baseline and 30 and 60 minutes after the infusion. Following the infusion of 3rd dose of [Trade Name], blood samples were drawn at ~~baseline and at 11 time points up to~~ regular intervals till day 28 ~~dose 3 after~~ to determine the pharmacokinetic parameters (see [Table 5](#)). The pharmacokinetic parameters based on baseline adjusted FXIII activity (Berichrom assay) are shown in Table 5.

Table 5: Pharmacokinetic Parameters (n=13) by Berichrom Assay Method - Baseline Adjusted Values

Parameters	Mean ±SD
AUC _{ss, 0-inf} (IU.hr/mL)*	184 ± 65
C _{ss, max} (IU/mL)	0.9 ± 0.2
C _{ss, min} (IU/mL)	0.05 ± 0.05
T _{max} (hr)	1.7 ± 1.4
Half-life [days]	6.6 ± 2.3
CL [mL/hr/kg]	0.25 ± 0.09
V _{ss} [mL/kg]	51.1 ± 12.6
MRT [days]	7.6 ± 1.8

AUC_{ss(0-inf)} = Area under the plasma concentration curve from time 0 to infinity at steady state

* 100% activity corresponds to 1 IU/mL

C_{ss, max}: Peak concentration at steady state

C_{ss, min}: Trough concentration at steady state

T_{max}: Time to peak concentration

CL: Clearance

V_{ss}: Volume of distribution at steady state

MRT = Mean residence time

SD = Standard deviation

Sponsor: In Table 5, please also report baseline non-adjusted PK parameters

Sponsor, please add the following in the PK section (after Table 5):

Due to small sample size, the impact of age, gender, and race on the pharmacokinetics of Factor XIII could not be reliably evaluated.

RECOMMENDATION

From pharmacokinetic perspective, the studies are acceptable. The sponsor should modify the clinical pharmacology labeling as suggested by the FDA.

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

Basil Golding, MD
Division Director, Division of Hematology
Office of Blood Review & Research

Study #1

Study Title: Pharmacokinetics, tolerability and viral safety of Factor XIII concentrate in healthy subjects.

This was a single center, single dose, prospective open trial. The primary objective of the study was to evaluate the pharmacokinetics of FXIII in healthy subjects. The secondary objective of the study was to assess safety of factor XIII with special reference to viral markers. There were 20 healthy male Caucasians subjects in this study. The mean age and body weights of the subjects were 25.5 years (18.9 to 34.9 years) and 77.7 kg (63 to 90 kg), respectively. FXIII was administered to subjects as a single bolus infusion (30 units/kg body weight). Blood samples were collected from the subjects at time 0, 10, 15, 30, and 60 minutes, 2, 4, 8, 24, and 48 hours, and on days 4, 9, 15, and 28 days. Factor XIII activity in plasma was determined at -----(b)(4)----- by a chromogenic test (Berichrom® F XIII), -----(b)(4)----- by a chromogenic test (Berichrom® F XIII), -----(b)(4)----- by a chromogenic test (Berichrom® F XIII). In order to calculate pharmacokinetic parameters, FXIII activity was transformed to concentrations in U/mL according to the following equation.

$$1\text{U/dL} = 1\%, 1\text{U/mL} = 100\%$$

For all subjects, FXIII activities (U/mL) were available for the pre-infusion sample and the pre-infusion values were subtracted from all subsequent FXIII activity values before pharmacokinetic calculation. The pharmacokinetic parameters were calculated by non-compartmental analysis and are shown in Table 1.

Table 1
Pharmacokinetic parameters of FXIII in healthy subjects (n = 20)

Parameters	Mean ± SD	Range
AUC (U.days/mL)	14.8 ± 10.4	2.6-36.5
Clearance (mL/h)	10.9 ± 9.5	2.6-43.8
Clearance (mL/hr/kg)	0.14 ± 0.11	0.03-0.49
Vss (liter)	5.34 ± 2.89	2.3-13.2
Half-life (days)	29 ± 36	2-119
MRT (days)	40 ± 49	4-165

Factor XIII activity against time in healthy subjects is shown in Figure 1 and Table 2. From Figure 1, it can be seen that Factor XIII activity in healthy subjects remain almost unchanged from 0.25 hour to day 4. In fact, the change in Factor XIII activity at 0.25 hour (169% activity) after the end of infusion and day 28 (672 hours, 122% activity) is only 28%. Factor XIII activity in healthy subjects returns to baseline value by day 28. The half-life of Factor XIII in healthy subjects is probably inaccurate due to the difficulty of estimating this parameter due to a flat

terminal phase. In short, in healthy subjects, Factor XIII appears to be a low clearance drug with a possibility of long half-life.

**Figure 1: Mean FXIII %activity vs time (mean baseline unadjusted)
in healthy subjects**

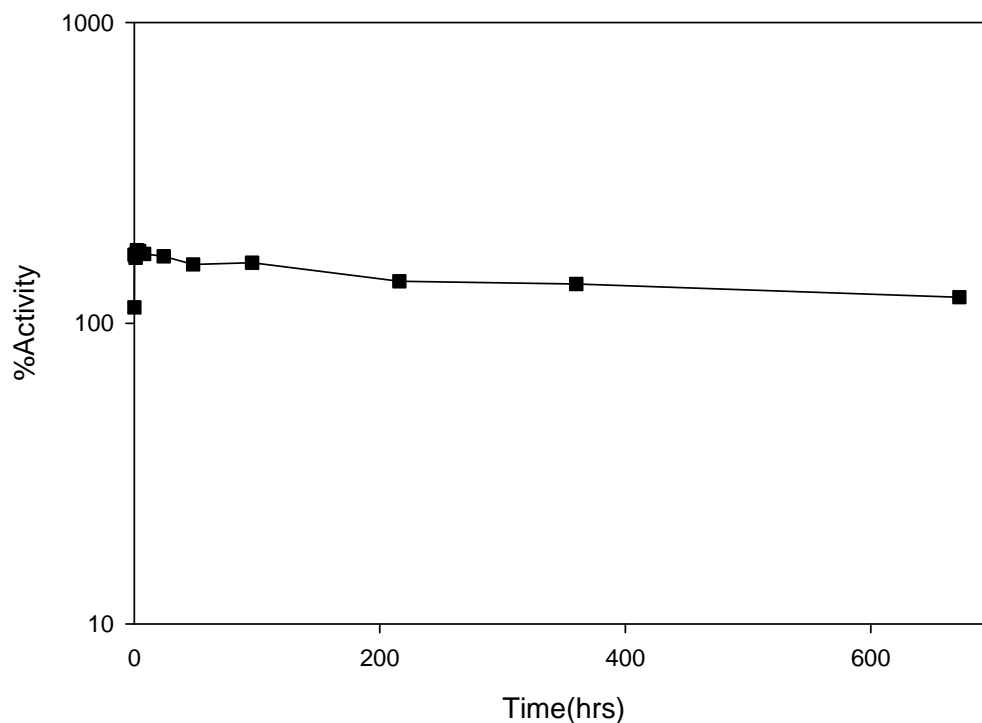


Table 2

Un-adjusted FXIII %activity (Mean \pm SD) vs time in healthy subjects

Time (hrs)	Factor XIII %activity
0	113 \pm 23
0.25	169 \pm 24
0.5	169 \pm 24
1	165 \pm 24
2	175 \pm 22
4	174 \pm 26
8	170 \pm 27
24	167 \pm 20
48	157 \pm 24
96	159 \pm 25
216	138 \pm 23
360	135 \pm 26
672	122 \pm 20

Study #2

Study Title: A 12-week, multicenter, pharmacokinetic and safety study of human plasma-derived factor XIII concentrate in subjects with congenital factor XIII deficiency.

The primary objective of this study was to evaluate the steady-state PK of Factor XIII Concentrate (Human) in subjects with congenital Factor XIII deficiency. The secondary objective of this study was to assess the safety of Factor XIII Concentrate (Human) administered over a period of 12 weeks in this population.

This was an open-label, single-arm, multicenter, PK study of Factor XIII Concentrate (Human) in subjects with congenital Factor XIII deficiency. The dose of Factor XIII Concentrate (Human) was 40 U/kg and it was administered every 4 weeks for a total of 3 doses over 12 weeks. The study design included a 4-week screening period and a 12-week treatment period. Thus, the duration of the study for an individual subject was approximately 16 weeks.

There were 13 subjects in the study (6 males and 7 females). There were 4 Caucasians, 5 African/Americans, 2 Asians and 2 Hispanics. The mean weight and age of the patients were 65 kg (19 to 102 kg) and 23 years (5 to 42 years), respectively. There were 5 patients <16 years of age and 8 >16 years of age.

Inclusion criteria: Subjects who were enrolled in the study had to meet all of the following inclusion criteria:

1. Written informed consent/assent for study participation obtained before undergoing any study-specific procedures,
2. Documented congenital Factor XIII deficiency that required prophylactic treatment with a Factor XIII containing product,
3. Males and females of any age with congenital Factor XIII deficiency, and
4. Received full hepatitis B vaccination and/or was hepatitis B surface antibody positive.

Exclusion criteria: Subjects meeting any of the following exclusion criteria were not enrolled into the study:

1. Diagnosis of acquired Factor XIII deficiency,
2. Administration of a Factor XIII-containing product, including blood transfusions or other blood products within 4 weeks prior to the planned Day 0,
3. Any known congenital or acquired coagulation disorder other than congenital Factor XIII deficiency,
4. Known or suspected to have antibodies towards Factor XIII,
5. Use of any other IMP within 4 weeks prior to the baseline visit (Day 0),
6. Positive result at screening for HIV,
7. Serum aspartate transaminase (AST) or serum alanine transaminase (ALT) concentration >2.5 times the upper limit of normal,

8. Fibrinogen < lower limit of normal,
9. Active bleeding,
10. Pregnant or breast feeding,
11. Intention to become pregnant during the course of the study,
12. Female subjects of childbearing potential not using, or not willing to use, a medically reliable method of contraception for the entire duration of the study,
13. Surgical procedure anticipated during the study period, and
14. Suspected inability (e.g., language problems) or unwillingness to comply with study procedures or history of noncompliance.

Subjects received 40 U/kg of Factor XIII Concentrate (Human) every 28 days for 3 doses administered as a bolus intravenous (IV) injection at 250 U/minute (when reconstituted 250 U/minute equals 4 mL/minute). The dose was not rounded up or down. Screening weight was used to calculate the size for all three doses. Investigational medicinal product (Factor XIII Concentrate [Human]) was administered based on units of Factor XIII Concentrate (Human); however, the analysis of Factor XIII levels was reported in International Units (IU). Assay results are described in IU and refer to the activity and antigen of Factor XIII in 1 mL of fresh human, pooled, citrated plasma (1 IU = Factor XIII in 1 mL plasma). Data in IU are based on a standard established by the “National Institute for Biological Standards and Control (NIBSC code 02/206)” in the United Kingdom. Accordingly, 100% activity of a reference plasma corresponds to 1 IU/mL.

For Dose 1 (Day 0) and Dose 2 (Day 28), blood samples for determination of Factor XIII level were obtained pre-infusion and 30 and 60 minutes after the end of the infusion. For Dose 3 (Day 56), blood samples for determination of Factor XIII level were obtained pre-infusion, and at the end of the infusion at 30 minutes, 60 minutes, 4 hours, 8 hours, 24 hours, 72 hours, 7 (± 1) days, 10 (± 1) days, 14 (± 1) days, 21 (± 1) days and 28 (± 1) days. In addition, blood samples were obtained for antibody testing as soon as possible after any bleeding episode. All samples for Factor XIII level testing were measured for both Factor XIII activity and antigen. The primary analysis of the PK of Factor XIII was baseline adjusted and assessed on the basis of measurements of Factor XIII activity using the Berichrom assay (photometric). As supplementary analyses, the PK of Factor XIII was assessed on the basis of measurements of Factor XIII activity using the -----(b)(4)----- test and the Berichrom® assay amended for background signal.

Factor XIII antibody testing was conducted at a central laboratory (---(b)(4)---) using validated methods. Samples with residual activity >75% were considered as having no Factor XIII inhibitors and were reported as negative. Samples with residual activity $\leq 75\%$ were considered as possibly having Factor XIII inhibitors. These samples were repeated in dilutions only if sample’s Factor XIII activity was $\leq 20\%$ of normal.

Comparison of results for all three assays showed high concordance, with Pearson correlation coefficients being ≥ 0.97 for all comparisons. There was a measurable level that was detected in

pre-dose samples. Consequently, levels were baseline adjusted by subtracting the pre-dose values. Pharmacokinetic evaluations were made using data for all assays both as baseline-adjusted and non-adjusted data.

Pharmacokinetic parameters were assessed individually for Factor XIII activity using a non-compartmental model. Standard formulae were used to calculate individual PK variables with and without adjustment of endogenous Factor XIII levels. The PK parameters for the non-adjusted data were generally higher for the standard activity than the amended activity assay and both were higher than the antigen assay. It should be noted that the mean standard half-life was skewed due to the result of 1 subject (Subject (b)(6)). The half-life for this subject was quite large (601 hr) with the standard activity assay, but was greatly reduced for the amended activity (168 hr). Because of the skewed results mentioned previously trends in the other parameters should be interpreted with caution.

Following an IV bolus administration of Factor XIII Concentrate (Human), measured levels generally rose for approximately 0.5 to 4 hours. After reaching peak level, measured levels fell in a mono-exponential fashion. Data from non-adjusted mean Factor XIII activity (both standard and amended assays) and antigen levels shows that the non-adjusted standard levels are generally higher than amended assay levels, and the antigen levels provide the lowest assessment of Factor XIII. Measured pre-dose (trough) levels on Day 28 (prior to administration of Dose 2), Day 56 (prior to administration of Dose 3), and Day 84 were generally constant suggesting that Factor XIII Concentrate (Human) administered every 4 weeks has reached to the steady-state following the third dose. The results of the pharmacokinetic study are summarized in Table 1 and Factor XIII activity vs time data are shown in Figure 1.

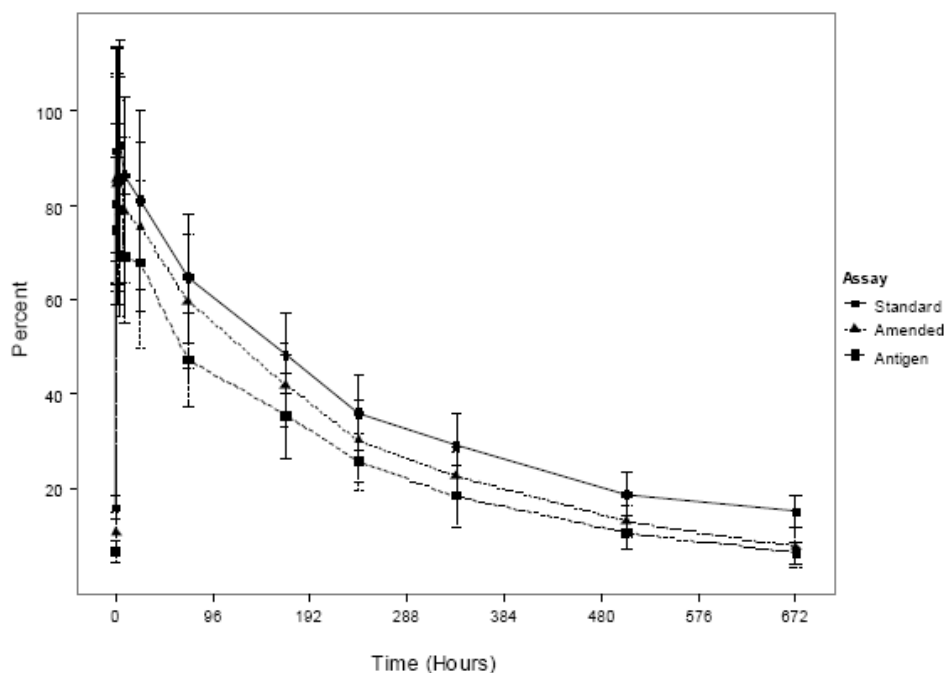
Table 1
Pharmacokinetic parameters of Factor XIII after dose 3

Parameters	Baseline non-adjusted			Baseline adjusted		
	Standard	Amended	Antigen	Standard	Amended	Antigen
C_{max}	0.99 ± 0.22	0.93 ± 0.22	0.85 ± 0.19	0.88 ± 0.20	0.88 ± 0.22	0.83 ± 0.18
C_{min}	0.15 ± 0.03	0.08 ± 0.04	0.06 ± 0.02	0.05 ± 0.05	0.05 ± 0.06	0.04 ± 0.02
$AUC_{(0-inf)}$	312 ± 66	222 ± 52	186 ± 47	184 ± 66	189 ± 67	158 ± 39
Clearance	0.13 ± 0.03	0.19 ± 0.05	0.23 ± 0.06	0.25 ± 0.09	0.25 ± 0.11	0.27 ± 0.07
Half-life	310 ± 112	200 ± 52	208 ± 57	158 ± 55	158 ± 60	159 ± 41
MRT	236 ± 13	211 ± 20	209 ± 14	183 ± 44	179 ± 47	194 ± 15
V_{ss}	58 ± 15	53 ± 12	67 ± 20	51 ± 13	50 ± 13	61 ± 19

Units of $AUC_{(0-inf)}$ = IU hr/mL; C_{max} and C_{min} = IU/mL; Clearance = mL/hr/kg; Volume of distribution at steady state (V_{ss}) = mL/kg, half-life and mean residence time (MRT) = hrs

The mean (\pm SD) Factor XIII trough levels 28 days following the third dose were 15.31% (\pm 3.449), 7.46% (\pm 4.347), and 6.15% (\pm 2.410) for the standard, amended, and antigen assays, respectively.

Figure 1: Mean Non-Adjusted Factor XIII Activity Versus Time Following Dose 3



Activity and antigen data were converted from IU/mL to percent by multiplying by 100.

Impact of age on the pharmacokinetics of Factor XIII:

There were 5 patients under age 16 years and 8 patients between 16 and 42 years of age in this study. The baseline adjusted $AUC_{(0-\infty)}$ and clearance (standard activity assay) of Factor XIII after the third dose in younger patients were 21% lower and 33% higher (based on body weight normalization to per kg) than the older patients. The half-life in younger patients was 35 hours shorter than the older patients (136 vs 171 hours). However, the sample size is too small to make any definitive conclusion about the impact of age on the pharmacokinetics of Factor XIII.

Impact of gender on the pharmacokinetics of Factor XIII:

There were 6 males and 7 females in this study. The baseline adjusted $AUC_{(0-\infty)}$ and clearance (standard activity assay) of Factor XIII were comparable between the two groups. The half-life in male patients was 21 hours longer than the female patients (169 vs 148 hours). The sample size is too small to make any definitive conclusion about the impact of gender on the pharmacokinetics of Factor XIII.

Impact of race on the pharmacokinetics of Factor XIII:

There were 4 Caucasians, 5 African Americans, 2 Asians and 2 Hispanics in this study. The baseline adjusted $AUC_{(0-\infty)}$ and clearance (standard activity assay) of Factor XIII were comparable between Caucasians and African Americans. However, AUC of Factor XIII was 17% and 61% lower in Asians and Hispanics, respectively. The clearance of Factor XIII in Caucasians, African Americans, Asians and Hispanics was 0.204, 0.194, 0.228, and 0.477 mL/hr/kg, respectively. The half-life of Factor XIII in Caucasians, African Americans, Asians and Hispanics was 203, 161, 114, and 103 hours, respectively. The sample size is too small to make any definitive conclusion about the impact of race on the pharmacokinetics of Factor XIII.

Primary efficacy variable:

There was no primary efficacy variable in this study. The surrogate endpoint for hemostatic efficacy was the effectiveness of the dosing regimen for Factor XIII Concentrate (Human) in achieving a trough Factor XIII level of $\geq 5\%$ over a period of 28 days. This surrogate efficacy endpoint is expected to be a predictor of the efficacy of Factor XIII Concentrate (Human) replacement therapy in preventing spontaneous bleeding episodes in a population of patients with congenital Factor XIII deficiency. Factor XIII level (based on the Berichrom™ photometric assay) at each time point and time associated with a Factor XIII level of $\geq 5\%$ and $\geq 10\%$ were estimated for each subject.

Achievement of Trough Factor XIII Level of $\geq 5\%$:

At baseline pre-infusion, a Factor XIII level of $\geq 5\%$ occurred in the majority of subjects in the PK population (12/13; 92.3%) based on the standard Berichrom assay. Activity assay results obtained by subtracting the background signal (amended Berichrom assay) yielded 5 subjects (38.5%) with a Factor XIII level of $\geq 5\%$ at baseline. At 30 and 60 minutes after the end of Dose 1, all subjects (100%) had a Factor XIII level of $\geq 5\%$ based on the standard and amended Berichrom assays.

With the exception of 1 subject, all subjects in the PK population had a Factor XIII level of $\geq 5\%$ based on the standard and amended Berichrom assays at pre-infusion (trough), 30 minutes, and 60 minutes after Dose 2 and Dose 3 (Day 28 and Day 56, respectively). One subject had a Factor XIII level of $< 5\%$ based on the amended Berichrom assay at pre-infusion (trough) before Dose 3 (Day 56). Plots of the percent of subjects with trough Factor XIII levels at least 5% (0.05 IU/mL) and at least 10% (0.10 IU/mL) at the baseline by study day for all three assays are presented in Figures 2 and 3, respectively. From Figure 2, it can be seen that at least 77% of subjects achieved the minimum required Factor XIII level, with the exception of Day 84 for the amended activity assay (61.5%). Based on the standard activity assay, all subjects maintained at least 10% activity at pretreatment on days 28 and 56, falling to 92.3% on day 84. Factor XIII Levels (%) at baseline, day 28, and day 56 are presented in Table 2.

Conclusions: In patients with factor XIII deficiency, the PK study indicates that Factor XIII has a low clearance and a long half-life (> 6 days). Based on 40 U/kg Factor XIII dose every 28 days, it

appears that in majority of subjects, a Factor XIII level of $\geq 5\%$ occurred (based on the standard Berichrom assay).

Figure 2: Percent of Subjects with Trough Factor XIII Levels $\geq 5\%$ at Baseline by Study Day

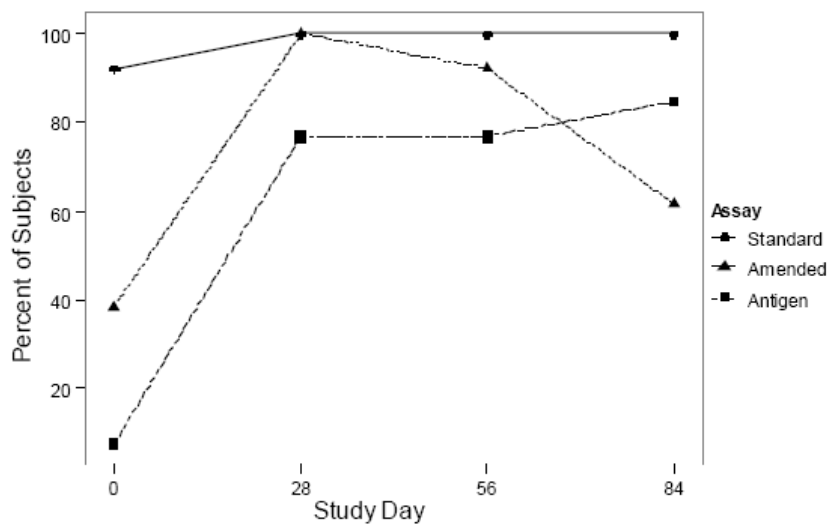


Figure 2: Percent of Subjects with Trough Factor XIII Levels $\geq 10\%$ at Baseline by Study Day

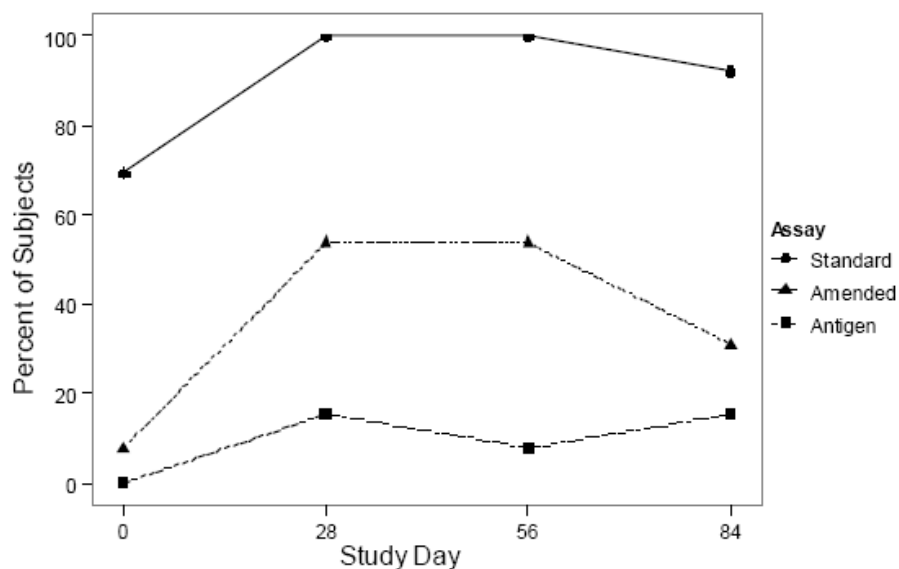


Table 2: Factor XIII Levels (%) at baseline, day 28, and day 56

Assay method	Pre-infusion	30 minutes*	60 minutes*
Baseline	(N = 13)	(N = 13)	(N = 12)
Standard activity	10.96 ± 4.32	87.62 ± 25.20	92.67 (31.1)
Amended activity	4.31 ± 4.23	82.38 ± 24.27	88.13 ± 31.21
Antigen	2.57 ± 1.76	72.15 ± 21.52	76.08 ± 21.16
Day 28	(N = 13)	(N = 13)	(N = 11)
Standard activity	15.69 ± 3.22	88.62 ± 31.78	83.82 ± 15.73
Amended activity	9.81 ± 3.81	84.23 ± 32.17	79.50 ± 17.02
Antigen	6.62 ± 3.75	75.15 ± 28.09	69.55 ± 10.01
Day 56	(N = 13)	(N = 13)	(N = 13)
Standard activity	16.08 ± 2.66	91.77 ± 21.90	90.46 ± 22.57
Amended activity	10.65 ± 4.09	85.54 ± 21.96	84.81 ± 22.83
Antigen	6.62 ± 2.29	80.31 ± 16.88	74.54 ± 15.78

*after the end of infusion