

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 46 of Regulation (EC) No1901/2006, as
amended**

**Fibrogammin P
Human Coagulation Factor XIII**

AT/W/0009/pdWS/001

**Marketing Authorisation Holder:
CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg**

Rapporteur:	AT
Finalisation procedure (day 90):	08.06.2011
Date of finalisation of PAR	28.07.2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Fibrogammin P
INN (or common name) of the active substance(s):	Human Coagulation Factor XIII
MAH:	CSL Behring GmbH Emil-von-Behring-Str. 76 35041 Marburg, DE
Currently approved Indication(s)	
Pharmaco-therapeutic group (ATC Code):	B02BD07
Pharmaceutical form(s) and strength(s):	powder and solvent for intravenous injection

I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed.

II. RECOMMENDATION¹

Based on the evaluation of Study BI 71023 it is concluded that no further dose adjustment is warranted for paediatric subjects, as further dose adjustment based on measured activity are sufficient.

The Rapporteur considers that the administration of FXIII in subjects with Congenital FXIII deficiency can be recommended.

III. INTRODUCTION

On 06.09.2010, the MAH submitted a completed paediatric study for Fibrogammin P 1250, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study do not influence the benefit risk for Fibrogammin P1250 and that there is no a consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

40 IU /kg Fibrogammin P1250 every 4 weeks was used in the submitted study.

Lyophilized powder containing approximately 1250 U / 30 mL vial to be reconstituted with 20 mL Sterile Water for Injection. The label of each vial noted the exact number of units of Factor XIII contained within that particular vial.

IV.2 Clinical aspects

1. Introduction

Fibrogammin P is approved for use in 12 countries and is marketed in 10 countries worldwide as of November 2010. Fibrogammin P has been marketed in countries of the EU since June 1993. Based on available data, total worldwide patient exposure is estimated to be 2.639.640 standard doses 750 U in the period from June 1993 through September 2010.

¹ The recommendation from section V can be copied in this section

The MAH submitted a final report for:

BI71023_2002 "A 12-week, Multicenter, Pharmacokinetic and Safety Study of Human Plasma-Derived Factor XIII Concentrate in Subjects with Congenital Factor XIII Deficiency

Clinical Background

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. 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.

The current therapeutic Indications are:

- Congenital deficiency of Factor XIII and resulting haemorrhagic diathesis, haemorrhages and disturbances in wound healing
- Haemorrhagic diatheses caused completely or in part by acquired Factor-XIII-deficiency
- Supportive therapy in case of disturbance in wound healing, especially in *ulcus cruris*, after large surgery or injuries.

The dose is:

1 ml is equivalent to 62.5 IU, and 100 IU are equivalent to 1.6 ml, respectively.

Important:

The amount to be administered and the frequency of administration should always be oriented towards the clinical efficacy in the individual case.

The following table can be used to guide dosing in bleeding episodes and surgery:

	Dosage International Units [IU] per kg body weight [b.w.]	Period for maintenance of FXIII level
Congenital FXIII deficiency	10	<i>Prophylaxis of haemorrhages:</i> approx. once a month. The interval is to be shortened if spontaneous haemorrhages develop.
	up to 35, reiterate injection when required to achieve an adequate FXIII level	Before surgery, required efficiency maintained by repeated injections until the wound has healed completely.
	10-20	<i>Therapy:</i> daily, for severe haemorrhages and extensive haematomas until bleeding has stopped.
Acquired FXIII deficiency	For treatment of haemorrhagic diatheses at least 15-20	Daily, until symptoms improve and normal FXIII levels are achieved spontaneously, respectively.

Supportive therapy in disorder of wound healing	10*	On the day of operation and once-daily on the following 3 days.
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* In high-risk patients the individual dose can be increased to 15-20 IU/kg b.w.

Acute bleeding episodes (including acquired deficiency states) will generally require considerably higher doses than routine prophylaxis in congenital disease. Due to the different pathogenesis of factor-XIII-deficiencies available data on half-lives differ considerably. Thus, it is recommended to monitor the increase in factor-XIII-activity with a factor-XIII-assay. In the case of major surgery and severe haemorrhages the aim is to obtain normal values.

2. Clinical study

BI71023_2002

➤ Description

“A 12-week, Multicenter, Pharmacokinetic and Safety Study of Human Plasma-Derived Factor XIII Concentrate in Subjects with Congenital Factor XIII Deficiency”

CSL Behring LLC, 1020 First Avenue, King of Prussia, PA 19406-0901, Clinical study report, Final 1.0/24 June 2010

➤ Methods

- Objective(s)

The primary objective of this study was to generate steady-state PK Factor XIII Concentrate (Human) data in subjects with congenital Factor XIII deficiency.

The secondary objective of this study was to assess the safety of Factor XIII Concentrate (Human) administration over a period of 12 weeks in this population.

In addition, the effect of Factor XIII Concentrate (Human) on a surrogate endpoint marker was investigated.

- Study design

open-label, single-arm, multicenter

- Study population /Sample size

Planned: 15 subjects

Analyzed: 14 subjects (safety population) and 13 subjects (PK population)

Demography:

14 patients with a mean age of 24 years entered into the study. In particular, the patients belonged to the following age classes:

EU classification:

- > 1 to < 2 years (infants and toddlers) 0
- > 2 to < 12 years (children) 3 (21.4%)
- > 12 to < 18 years (adolescents) 5 (35.7%)
- > 18 to < 65 years (adults) 6 (42.9%)
- > 65 (geriatrics) 0

- Treatments

Subjects received 40 U/kg of Factor XIII Concentrate (Human) per administration every 28 days for 3 doses administered as a bolus intravenous (IV) injection at 250 U/minute.

- Outcomes/endpoints

primary objective: steady-state pharmacokinetic (PK)

secondary objective: safety of three doses of Factor XIII Concentrate (Human) administration over a period of 12 weeks

surrogate endpoint: trough Factor XIII level of $\geq 5\%$

- Statistical Methods

The primary analysis of the PK of Factor XIII was baseline adjusted for pre-infusion levels and assessed on the basis of measurements of Factor XIII activity using the Berichrom® assay. As supplementary analyses, the PK of Factor XIII was assessed without baseline adjustment and also on the basis of measurements of Factor XIII levels using the Berichrom™ activity assay amended for background signal and the Affinity biological antigen Enzyme-Linked Immuno Sorbent Assay (ELISA) test.

Factor XIII levels (based on all three assays) at each time point and time associated with a Factor XIII level of $\geq 5\%$ and $\geq 10\%$ were estimated for each subject and summarized.

Descriptive statistics were used to summarize Factor XIII levels for the overall study population and by gender, age, and race.

Pharmacokinetic parameters were assessed individually for Factor XIII activity using a non-compartmental model. Standard formulae (e.g., built-in in WinNonlin®) were used to calculate individual PK variables without and with adjustment for endogenous Factor XIII levels.

The following steady-state PK parameters were calculated using non-compartmental methods as data permitted following Dose 3: peak concentration at steady-state ($C_{ss, \max}$); trough concentration at steady-state ($C_{ss, \min}$); time to peak concentration (T_{\max}); incremental recovery; terminal half-life ($t_{1/2}$); area under the curve at steady-state (AUC_{ss}); clearance (CL/f); volume of distribution at steady-state (V_{ss}); and mean residence time (MRT).

Treatment-emergent AEs were summarized for the following: AEs; SAEs; treatment-related; by maximum relationship to Factor XIII, occurring within 24 hours and occurring 72 hours from the end of infusion of study treatment; by maximum severity, occurring within 72 hours from the end of infusion of study treatment; by maximum relationship to Factor XIII; by maximum severity; and by size of single dose (total units administered). Treatment-emergent AEs leading to premature discontinuation and fatal AEs were listed by subject.

Results for selected laboratory parameters were summarized by visit using descriptive statistics, including change from baseline to the smallest, largest, and final values after the first dose of study treatment. For laboratory parameters with positive or negative results (e.g., antibody testing), the number and proportion with positive treatment-emergent results were summarized at each visit.

The number and proportion of subjects with treatment-emergent abnormal laboratory values (normal baseline value and abnormal [i.e., met Grade 3 or 4, CTCAE v. 3.0] post-baseline value) were tabulated by laboratory parameter.

The number and proportion of subjects with treatment-emergent potentially clinically significant vital sign values on dosing days were tabulated. Selected vital signs results and/or change from baseline values were also summarized by visit and time point using descriptive statistics.

The number and proportion of subjects with changes from baseline (normal finding at baseline to abnormal finding after the first administration of study treatment) in physical examination findings were tabulated.

➤ Results

• Recruitment/ Number analysed

Among subjects in the safety population, half were female (50.0%). Approximately one-third (35.7%) of the subjects were Caucasian and one-third (35.7%) Black/African American. At screening, the mean age was 24.0 years and the majority of subjects (64.3%) were 16 to <65 years of age.

The mean age at diagnosis was 6.3 years, with 85.7% of subjects <16 years of age. Five subjects were <16 years of age at screening. Subject 13004 was 5 years of age, Subject 13005 was 11 years of age, Subject 24006 was 8 years of age, Subject 24007 was 12 years of age, and Subject 24010 was 14 years of age.

Demographic Data at Enrollment (Safety Population)

(N=14)

Age at Screening (years) Mean (SD)		
Median (range)	24.0 (12.55)	26.5 (5 – 42)
Age group at Screening (n, %)		
<16 years	5 (35.7)	
16 to <65 years	9 (64.3)	
≥65 years	0	
Gender (n, %) Male Female		
	7 (50.0)	7 (50.0)
Race (n, %)		
Caucasian	5 (35.7)	
Black/African-American	5 (35.7)	
Asian	2 (14.3)	
Hispanic	2 (14.3)	
Other	0	
Height (cm) Mean (SD) Median (range)		
	158.3 (18.40)	162.6 (108 – 177)
Weight (kg) Mean (SD) Median (range)		
	67.69 (21.835)	73.10 (18.5 – 102.1)
Age at Diagnosis (years) Mean (SD)		
Median (range)	6.3 (7.91)	4.5 (0 – 26)
Age group at Diagnosis (n, %)		
<16 years	12 (85.7)	
16 to <65 years	2 (14.3)	
≥65 years	0	

- Efficacy results

Evaluation of the Factor XIII activity by the standard activity assay showed that all subjects had $\geq 5\%$ activity at pre-infusion (trough) on Day 28 and Day 56. Following the third dose, a Factor XIII activity trough level of $\geq 5\%$ occurred in all subjects and $>10\%$ in 92.3% of subjects based on the standard Berichrom assay. The amended activity and antigen assay results also demonstrate that the majority of subjects had $\geq 5\%$ activity at the predose (trough) time points.

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

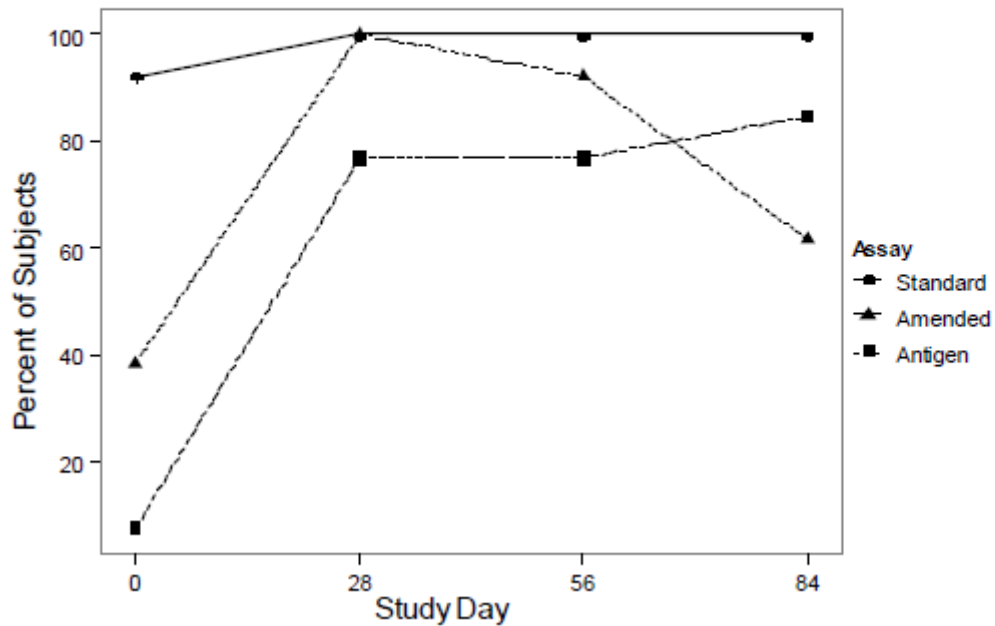
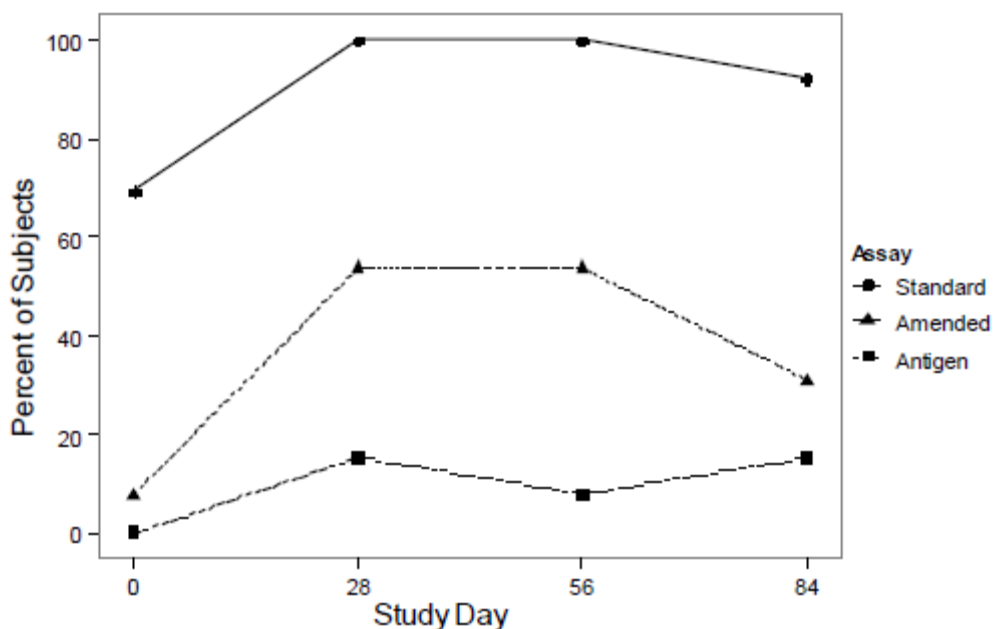


Figure 3. Percent of Subjects with Trough Factor XIII Levels $\geq 10\%$ at Baseline by Study Day



The mean (\pm SD) trough Factor XIII trough levels 28 days following the third dose were 15.31% (± 3.449), 7.46% (± 4.347), and 6.15% (± 2.410) for the standard, amended, and antigen assays, respectively, supporting that the Factor XIII replacement coverage is adequate with the dose regimen employed in the present study.

Table 14.2.1.2 Summary of FXIII Levels (%) by Visit and Time Point (PK Population)

Visit Time Point	All Subjects (N=13)		
	Standard Activity [1]	Amended Activity [2]	Antigen
Day 56			
14 +/- 1 days after DOSE 3			
n	13	13	13
Mean (SD)	29.08 (6.763)	22.65 (4.854)	18.38 (6.564)
Median	28.00	22.00	17.00
25%, 75%	25.00, 30.00	19.50, 26.00	15.00, 19.00
Min, Max	21.0, 44.0	16.0, 32.0	10.0, 38.0
21 +/- 1 days after DOSE 3			
n	13	13	13
Mean (SD)	18.77 (4.512)	13.04 (3.230)	10.69 (3.497)
Median	18.00	14.00	10.00
25%, 75%	18.00, 20.00	11.50, 15.00	9.00, 11.00
Min, Max	11.0, 30.0	5.0, 18.5	5.0, 18.0
28 +/- 1 days after DOSE 3			
n	13	13	13
Mean (SD)	15.31 (3.449)	7.46 (4.347)	6.15 (2.410)
Median	17.00	7.00	6.00
25%, 75%	12.00, 18.00	4.00, 11.00	4.00, 7.00
Min, Max	9.0, 20.0	1.0, 14.5	3.0, 10.0

[1] Standard activity as determined by the Standard Berichrom assay

[2] Amended activity as determined by adjustment of the standard Berichrom assay for background signal.

Assessor's comments on overall efficacy: The surrogate efficacy endpoint has been demonstrated. However the study population was relatively small.

Pharmacokinetic results

Comparison of results for all three assays showed high concordance with Pearson correlation coefficients being ≥ 0.97 for all comparisons. A strong correlation exists between the standard activity and amended activity assays (Pearson's correlation coefficient 0.996; $p < 0.001$).

The baseline-adjusted mean values for AUC, T_{max}, half-life, CL, and MRT were 184.010 IU*hr/mL, 1.719 hr, 157.636 hr, 0.246 mL/hr/kg, and 239.944 hr, respectively, for Factor XIII Concentrate (Human) using the standard activity assay. The baseline-adjusted mean value for C_{ss, max} for the standard assay was 0.877 IU/mL, which did not exceed those seen in subjects without Factor XIII deficiency (normal range: 0.70 to 1.40 IU/mL).

Baseline-Adjusted Pharmacokinetic Parameters After Dose 3 (Pharmacokinetic Population)

(N=13) Parameter (unit)	Standard Activity	Amended Activity	Antigen
AUC_{ss, 0-inf} (IU*hr/mL)			
Mean (SD)	184.010 (65.7800)	188.660 (67.4563)	158.034 (39.0038)
Geometric mean	173.146	176.247	153.729
CV (%)	38.087	41.925	24.823
Median	170.315	191.068	160.919
Min, Max	87.90, 300.22	77.72, 301.45	103.41, 243.51
95% CI (geometric mean)	138.619, 216.273	138.202, 224.764	132.612, 178.210
C_{ss, max} (IU/mL)			
Mean (SD)	0.877 (0.2040)	0.882 (0.2206)	0.825 (0.1813)
Geometric mean	0.855	0.857	0.805
CV (%)	23.867	25.594	23.730
Median	0.880	0.885	0.819
Min, Max	0.60, 1.22	0.59, 1.30	0.52, 1.12
95% CI (geometric mean)	0.741, 0.985	0.736, 0.998	0.699, 0.928
C_{ss, min} (IU/mL)			
Mean (SD)	0.050 (0.0475)	0.045 (0.0568)	0.036 (0.0183)
Geometric mean	0.049	0.001	0.031
CV (%)	104.253	not defined	69.423
Median	0.050	0.010	0.030
Min, Max	0.00, 0.16	0.00, 0.15	0.01, 0.06
95% CI (geometric mean)	0.027, 0.091	0.000, 8.030	0.021, 0.045
T_{max} (hr)			
Mean (SD)	1.719 (1.4393)	1.759 (1.4275)	3.526 (5.8850)
Geometric mean	1.314	1.356	1.723
CV (%)	83.436	82.737	158.677
Median	1.183	1.183	1.183
Min, Max	0.53, 4.23	0.53, 4.23	0.53, 22.38
95% CI geometric mean	0.847, 2.038	0.876, 2.098	0.875, 3.394
Incremental Recovery_{ss} (IU/mL/IU/kg)			
Mean (SD)	0.022 (0.0051)	0.022 (0.0055)	0.021 (0.0045)
Geometric mean	0.021	0.021	0.020
CV (%)	23.841	25.568	23.675

Median	0.022	0.022	0.020
Min, Max	0.02, 0.03	0.01, 0.03	0.01, 0.03
95% CI geometric mean	0.019, 0.025	0.018, 0.025	0.017, 0.023
Incremental Recovery_{0-30 min}			
(IU/mL/IU/kg)			
Mean (SD)	0.020 (0.0052)	0.020 (0.0055)	0.019 (0.0040)
Geometric mean	0.020	0.020	0.019
CV (%)	26.341	28.137	21.939
Median	0.019	0.021	0.019
Min, Max	0.01, 0.03	0.01, 0.03	0.01, 0.03
95% CI geometric mean	0.017, 0.023	0.017, 0.023	0.017, 0.022
Incremental Recovery_{0-60 min}			
(IU/mL/IU/kg)			
Mean (SD)	0.022 (0.0051)	0.022 (0.0055)	0.020 (0.0039)
Geometric mean	0.021	0.021	0.020
CV (%)	23.523	25.249	21.442
Median	0.022	0.022	0.020
Min, Max	0.02, 0.03	0.01, 0.03	0.01, 0.03
95% CI geometric mean	0.018, 0.024	0.018, 0.024	0.017, 0.022
Half-life (hr)			
Mean (SD)	157.636 (54.9722)	157.572 (59.6339)	159.231 (41.4915)
Geometric mean	148.699	147.788	154.060
CV (%)	37.381	38.396	27.793
Median	158.226	142.959	157.740
Min, Max	73.52, 264.45	85.43, 274.75	84.80, 236.18
95% CI geometric mean	119.507, 185.022	118.118, 184.910	130.648, 181.667
CL (mL/hr/kg)			
Mean (SD)	0.246 (0.0932)	0.246 (0.1134)	0.268 (0.0651)
Geometric mean	0.231	0.227	0.260
CV (%)	38.107	41.935	24.815
Median	0.236	0.210	0.249
Min, Max	0.13, 0.46	0.13, 0.51	0.16, 0.39
95% CI geometric mean	0.185, 0.289	0.178, 0.290	0.225, 0.302
V_{ss} (mL/kg)			
Mean (SD)	51.056 (12.6111)	50.115 (13.3899)	60.519 (19.1944)
Geometric mean	49.585	48.414	57.861
CV (%)	25.870	28.278	31.964
Median	50.833	51.739	59.338
Min, Max	31.65, 70.70	31.61, 73.04	31.76, 101.31
95% CI geometric mean	42.516, 57.829	40.943, 57.248	47.922, 69.862
MRT (hr)			
Mean (SD)	239.944 (82.7866)	244.377 (90.56.40)	235.084 (43.0515)
Geometric mean	227.415	229.943	231.529
CV (%)	34.997	37.177	18.274
Median	240.662	211.603	236.279
Min, Max	137.53, 408.40	147.06, 421.75	172.17, 316.32
95% CI geometric mean	185.188, 279.270	185.009, 285.790	207.510, 258.328

No accumulation of FXIII Concentrate (Human) would be expected with the proposed dose regimen.

Baseline-Adjusted Accumulation Factor After Dose 3 (Pharmacokinetic Population)

(N=13)

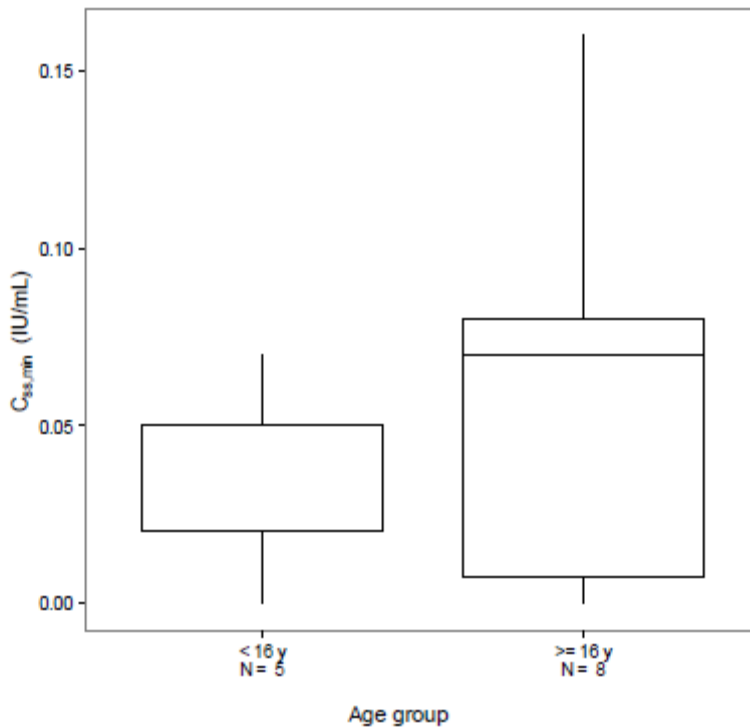
Parameter (unit)	Standard Activity	Amended Activity	Antigen
R_{ss}			
Mean (SD)	1.0671 (0.0619)	1.0690 (0.0703)	1.0647 (0.0474)
Geometric mean	1.0655	1.0669	1.0637
CV (%)	5.807	6.590	4.555
Median	1.0581	1.040	1.055
Min, Max	1.0018, 1.2075	1.004, 1.225	1.004-1.161
95% CI geometric mean	1.004, 1.190	1.006, 1.209	1.010, 1.152

Evaluation by Age

The baseline-adjusted C_{ss}, min stratified by age showed lower median values for the younger subjects (0.020 IU/mL) than for older subjects (0.070 IU/mL), although the distribution is wider for the older subjects. The mean C_{ss}, min values were 0.032 and 0.061 IU/mL for the younger and older subjects, respectively.

Comparisons of both baseline-adjusted and non-adjusted PK parameters by age, gender, and race suggest that the weight-normalized clearance is somewhat higher for paediatric subjects than for adults. This finding is consistent with published findings that while clearance is typically lower in paediatric subjects than adults, when normalized by body weight, the clearance for paediatric subjects is higher. Consequently, when the dose is administered based on body weight, summary measures of exposure such as AUC, C_{ss}, max and C_{ss}, min will be lower for paediatric subjects than for adults.

Figure 6. Box and Whisker Plot of Baseline-Adjusted $C_{ss, min}$ by Age for the Standard Activity Assay



**Table 14.2.4.4 Summary Statistics of Pharmacokinetic Parameters [1] by Gender and Age - Baseline Adjusted Values
Outliers Excluded
(PK Population)**

Parameter (unit)	Males (N=6)	Females (N=7)	Age <16 Years (N=5)	Age 16-<65 Years (N=8)	Age >=65 Years (N=0)
FXIII Standard Activity [2]					
$C_{ss, min}$ (IU/mL)*					
n	6	7	5	8	
Mean (SD)	0.058 (0.0546)	0.043 (0.0439)	0.032 (0.0277)	0.061 (0.0554)	
Geometric mean	0.038	0.072	0.034	0.062	
CV (%)	137.954	33.227	71.290	121.656	
Median	0.045	0.050	0.020	0.070	
Min, Max	0.01, 0.16	0.00, 0.11	0.00, 0.07	0.00, 0.16	
95% CI (geometric mean)	0.013, 0.112	0.043, 0.121	0.012, 0.095	0.023, 0.169	
T_{max} (hr)					
n	6	7	5	8	
Mean (SD)	0.994 (0.2586)	2.340 (1.7640)	0.863 (0.3664)	2.254 (1.6200)	
Geometric mean	0.963	1.715	0.807	1.782	
CV (%)	29.596	111.419	42.249	84.197	
Median	1.117	1.400	0.667	1.200	
Min, Max	0.63, 1.22	0.53, 4.23	0.53, 1.40	0.70, 4.23	
95% CI (geometric mean)	0.710, 1.305	0.747, 3.936	0.488, 1.334	0.966, 3.286	

[1] Table includes PK parameters calculated after dose 3 (day 56).
 [2] Standard activity as determined by the Standard Berichrom assay
 [3] Amended activity as determined by adjustment of the standard Berichrom assay for background signal.
 [4] Incremental recovery (U/mL/U/kg) is defined as maximum (peak) FXIII activity (U/mL) obtained following infusion, per dose of (U/kg) infusion. Incremental recovery 0-30 and 0-60 uses the peak activity level obtained through 30 and 60 minutes, respectively.
 Note: CV (%) = $100 \cdot \sqrt{\exp(\text{SDlog}) - 1}$ where SDlog is standard deviation of log-transformed values. Outliers for two patients are excluded from calculation of PK parameters.
 * $C_{ss, min}$ results from patients with a minimum value of 0 are excluded from the calculation of the geometric mean and CI and SDlog.
 Note: C_{max} = maximum change from baseline; C_{min} = minimum change from baseline.

Assessors comment overall pharmacokinetic: The PK-parameters are comparable with previously published reports.

- Safety results

This 12-week, 3-dose clinical study of Factor XIII Concentrate (Human) supports a favorable safety profile. Analyses of AEs, laboratory, and physical examination data revealed no safety issues of concern. Eight subjects (57.1%) reported at least one treatment-emergent AE during the study. Two subjects (14.3%) reported possibly related AEs (thrombin-antithrombin III complex increased and prothrombin increased [verbatim term: elevated prothrombin fragment] in 1 subject and fibrin D-dimer increased in 1 subject). All AEs were mild or moderate in severity. The most frequently reported treatment-emergent AE was acute bronchitis (14.3%).

Overview of Subjects with Treatment-Emergent Adverse Events (Safety Population)

	n (%)
	(N=14)
Any treatment-emergent AE	8 (57.1)
Any treatment-related AE ¹	2 (14.3)
Fatal (AE outcome)	0
Any serious adverse event	0
Any AE leading to study withdrawal	0
¹ Treatment-related AEs included those whose relationship to study treatment was related, possibly related or missing	

Subjects with Treatment-Emergent Adverse Events (Safety Population)

	n (%) (N=14)
Any treatment-emergent AE	8 (57.1)
Infections and infestations	5 (35.7)
Acute bronchitis	2 (14.3)
Flu	1 (7.1)
Infected sebaceous cyst	1 (7.1)
Tinea corporis	1 (7.1)
Urinary tract infection	1 (7.1)
Injury, poisoning and procedural complications	4 (28.6)
Ankle injury	1 (7.1)
Bruising of arm	1 (7.1)
Contusion of knee	1 (7.1)
Contusion of toe	1 (7.1)
Investigations	2 (14.3)
Fibrin D-dimer increased	1 (7.1)
Prothrombin increased	1 (7.1)
Thrombin-antithrombin III complex increased	1 (7.1)
Skin and subcutaneous tissue disorders	2 (14.3)
Ecchymosis	1 (7.1)
Rash	1 (7.1)
Metabolism and nutrition disorders	1 (7.1)
Borderline diabetes	1 (7.1)
Reproductive system and breast disorders	1 (7.1)
Penile adhesion	1 (7.1)

Assessors comment overall safety: FXIII was consistently safe and well-tolerated in the subjects

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The one study described in this overview was designed as pivotal clinical trial in the clinical development program of Factor XIII (human) to obtain a marketing authorisation in the USA.

The aim of this study was to provide 12 weeks of safety and steady-state pharmacokinetic (PK) data with respect to the prophylactic administration of factor XIII Concentrate in subjects with congenital Factor XIII deficiency. The data from this study revealed no concerns in the pharmacokinetics or safety of FXIII.

The safety profile of FXIII observed in the study is consistent with that in the existing Reference Safety Information for FXIII and does not indicate a need to make any changes to the current approved product information.

The MAH concluded that Hemostatic efficacy of the dosage regimen utilized in this study will be confirmed in an ongoing, 1-year, 40-subject, efficacy and safety study (BI 71023)”

Based on the evaluation of Study BI 71023 it is concluded that no further dose adjustment is warranted for paediatric subjects, as dose adjustment based on measured activity are sufficient.

➤ Recommendation

After evaluating the presented data the Rapporteur considers that the administration of FXIII in subjects with congenital FXIII deficiency can be recommended according to the current SmPC.

No further action required.