



STATISTICAL REVIEW AND EVALUATION BLA (FINAL REVIEW)

BLA Number: STN 125385/0

Product Name: FXIII Concentrate (Human)

Indication(s): Routine prophylactic treatment of congenital FXIII deficiency

Applicant: CSL Behring

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1. EXECUTIVE SUMMARY

The sponsor submitted a biologic licensure application for the use of Factor XIII (FXIII) Concentrate (Human) for the prophylactic treatment of congenital FXIII deficiency, an extremely rare (estimated 100 patients in the US), serious, and life-threatening condition. The sponsor is applying for approval via the accelerated approval process. The clinical development program consisted of two studies (a Phase 2 PK study with a surrogate clinical endpoint and a Phase 3b confirmatory study of the surrogate endpoint to be started prior to the marketing submission). Three other efficacy studies provide supporting efficacy evidence. The safety program consists of 12 clinical studies: the five efficacy studies plus seven additional supportive studies in various populations (one in healthy volunteers, four in congenital Factor XIII deficiency, and two in -----(b)(4)-). See Table 1 for a synopsis of all 12 clinical studies.

The sponsor submitted a safety update for Studies 3001 and 3002 for the 7.5 months after the data cut for the original submission. This updated safety data are included in this review.

The primary efficacy endpoint is a PK endpoint (trough FXIII activity level of $\geq 5\%$). The surrogate endpoint in the ongoing confirmatory study (incidence density through Week 52 of spontaneous bleeding events requiring administration of a Factor XIII-containing product to treat the bleeding event) currently shows an incidence of zero (four spontaneous bleeding events that did not require FXIII treatment). One out of 132 (0.76%) unique subjects in the nine clinical studies demonstrated transient FXIII inhibitor development.

This reviewer has no objections to the approval of FXIII Concentrate (Human).

2. INTRODUCTION

2.1 Overview

The sponsor submitted a biologic licensure application for the use of Factor XIII (FXIII) concentrate (Human) for the prophylactic treatment of congenital FXIII deficiency, an extremely rare (estimated 100 patients in the US), serious, and life-threatening condition. The life-threatening consequences of congenital FXIII deficiency require prophylactic administration of FXIII as soon as the diagnosis is established. The National Hemophilia Foundation's Medical and Scientific Advisory Council recommends FXIII for the treatment of FXIII deficiency even though it is not licensed in the US, Canada or Spain.

FXIII is an endogenous plasma glycoprotein consisting of two A-subunits and two B-subunits. FXIII circulates in blood plasma and is present in platelets, monocytes, and macrophages. It appears in two forms: a heterotetrameric (A_2B_2) plasma protein and a homodimeric (A_2) cellular form. FXIII is a proenzyme that is activated in the presence of calcium ions by thrombin cleavage of the A-subunit. Intracellularly, the homodimeric form (A_2) of only the A-subunits is found and the B-subunits have no enzymatic activity

in plasma. FXIII is essential for normal coagulation, wound healing, and the physiological protection of the clot against fibrinolysis.

The sponsor's FXIII Concentrate (Human) is presently licensed in 13 countries and has been marketed since 1993. The general trade name outside of the US is Fibrogammin P. FXIII Concentrate (Human) is a sterile, preservative free, heat-treated, lyophilized FXIII concentrate made from pooled human plasma. After reconstitution with sterile water for injection, it is administered intravenously. Each single use vial contains 1000-1600 IU FXIII, 120-200 mg human albumin, 120-320 mg total protein, 80-120 mg glucose, and 140-220 mg sodium chloride.

The sponsor is applying for approval via the accelerated approval process. The sponsor and CBER agreed (pre-IND meeting on October 10, 2008) to a clinical development program consisting of two studies (a PK study with a surrogate clinical endpoint and a confirmatory study of the surrogate endpoint to be started prior to the marketing submission) which would be supported along with the results from earlier studies. These two studies, along with all other supportive studies are summarized in Table 1.

Table 1: Efficacy and Safety Studies to Support the BLA

<i>Study #</i>	<i>Design</i>	<i>Population</i>	<i>N</i>	<i>Purpose</i>
<i>Efficacy Studies</i>				
2002	Prospective, open-label, multicenter, single-arm	Congenital FXIII deficiency	14	PK, safety, efficacy (pivotal study) (Phase 2)
3001	Prospective, open-label, multicenter, single-arm	Congenital FXIII deficiency	41 (ongoing; enrollment complete)	Long-term efficacy, safety, PK (Phase 3b; post-marketing)
3002	Prospective, open-label, multicenter, single-arm	Congenital FXIII deficiency	24 (ongoing); max 80	Provide study drug to US patients until drug commercially available; long-term safety; observational efficacy
5001	Prospective, open-label, multicenter; single-arm	Congenital FXIII deficiency	19	efficacy, safety (Phase 4)
5986	Prospective, open-label, multicenter, uncontrolled	Congenital FXIII deficiency	72 (ongoing); max 80	Safety; efficacy (bleeding narratives only) (Phase 2/3)
<i>Safety Studies</i> <i>(in addition to the above efficacy studies)</i>				
1003	Prospective, open-label, uncontrolled	Healthy volunteers	20	PK/PD/safety (Phase 1)
7D-101PK	Prospective, randomized, active-	Congenital FXIII	1	BE/PK/PD/safety (pilot study)

<i>Study #</i>	<i>Design</i>	<i>Population</i>	<i>N</i>	<i>Purpose</i>
<i>Efficacy Studies</i>				
	controlled crossover	deficiency		
7MN-101PK	Prospective, randomized, active-controlled crossover	Congenital FXIII deficiency	13	BE/PK/PD/safety
7MN-101PK (Extension)	Prospective, open-label, uncontrolled	Congenital FXIII deficiency	2	PK/PD/safety (long-term follow-up)
201	Open-label, uncontrolled	Congenital FXIII deficiency	4	PK/PD/safety
301CL	Prospective, randomized, placebo-controlled, multicenter, two- arm	----- -(b)(4)-----	28	Safety (Phase 3)
302CL	Prospective, randomized, placebo-controlled, multicenter, three-arm	----- -(b)(4)-----	33	Safety (Phase 3)

2.2 Data Sources

All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

SAS efficacy data sets were provided for the pivotal study (2002) and two of the supporting studies (3001 and 3002). One SAS safety data set was provided for study 5986.

3. STATISTICAL EVALUATION

As agreed upon during the pre-BLA meeting (March 10, 2010), the sponsor provided a separate summary of efficacy and safety for each individual study in Module 2, instead of an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), as recommended by the FDA Guidance for Industry *Integrated Summaries of Effectiveness and Safety: Location within the Common Technical Document*.

3.1 Evaluation of Efficacy

The efficacy program consists of five clinical studies: one pivotal study (**Study 2002**) and four supportive studies (**Studies 3001, 3002, 5001, 5986**).

3.1.1 Study 2002 (Pivotal Study)

Primary objective: generate steady-state PK data for the study treatment.

Secondary objective: assess the safety of the study treatment over a period of 12 weeks.

3.1.1.1 Study Design and Endpoints

This Phase 2, multicenter, prospective, open-label, single-arm study is complete. The subjects were to receive 40 IU/kg every four weeks for a total of three doses over 12 weeks. Baseline weight was used to calculate the dose for all three treatments.

Male or female subjects of any age with congenital FXIII deficiency were eligible. Taking into account an estimated discontinuation rate of 20%, targeted enrollment was approximately 15 subjects to obtain 12 evaluable subjects; 14 subjects were actually enrolled. No hypothesis testing was proposed; therefore the sample size was predicated on the number of subjects (12) needed to provide adequate information for the generation of an accurate PK profile.

This study did not have a primary hemostatic efficacy endpoint. Rather, the surrogate efficacy endpoint is the steady state PK profile of the study treatment, measured after the third dose. The efficacy variable measured is the achievement of a trough FXIII activity level of $\geq 5\%$. This surrogate efficacy endpoint of trough FXIII activity levels is believed to predict the hemostatic efficacy of the FXIII Concentrate (Human) replacement therapy in preventing spontaneous bleeding episodes. The primary analysis of the PK of FXIII is assessed on the basis of measurement of FXIII activity using the standard Berichrom assay test.

A secondary endpoint is the evaluation of the safety of the administration of the study treatment in the FXIII population. Safety assessments included AEs, laboratory assessments, vital signs, and physical examinations.

The study design includes a four week screening period and a 12 week treatment period, yielding an individual subject study duration of 16 weeks.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

Of the 15 subjects screened, 14 were enrolled, 13 completed the study and one discontinued due to withdrawal of consent; this subject received only two doses of study treatment.

The safety analysis population consists of all subjects who received a dose of study treatment. The primary analysis (PK) population consists of all subjects in the safety population who completed the study.

Among subjects in the safety population, half of the 14 subjects were female (50.0%). Approximately one-third (35.7%) each were Caucasian and Black/African American; two subjects (14.3%) each were Asian and Hispanic. At screening, the mean age was 24.0 years and the majority of subjects were 16 to <65 years of age.

At baseline pre-infusion, 92.3% (12/13) of the subjects had a FXIII activity level of $\geq 5\%$ based on the standard Berichrom assay.

3.1.1.3 Statistical Methodologies

No formal testing of hypotheses was planned. Tabular data summaries were presented to provide an overview of the PK and safety findings. Descriptive statistics (mean, SD, median, range, quartiles) were planned for continuous variables, and frequency and percentage for categorical variables. Data was to be summarized using the safety population, but if the safety and PK populations were different, the data would be summarized separately for the PK population.

For all analyses, the baseline value was defined as the last non-missing value obtained prior to the first administration of study treatment. If this value was missing or unavailable, then an available screening result would be used. The sponsor did not plan to implement any procedure for replacing missing data.

3.1.1.4 Results and Conclusions

As the study did not have a primary hemostatic efficacy endpoint, no efficacy conclusions are made. However, it is noted that no bleeding events occurred during the study.

3.1.2 Study 3001 (Supporting Study)

Primary objective: collect and evaluate observational long-term efficacy data with regard to the frequency and severity of bleeding episodes

Secondary objectives:

- evaluate the association between Factor XIII activity peak and trough levels and the incidence of spontaneous bleeding events requiring treatment
- collect and evaluate additional long-term PK data
- evaluate hemostatic efficiency in treatment of acute bleeding events and for surgery prophylaxis
- collect and evaluate long-term safety data.

3.1.2.1 Study Design and Endpoints

This multicenter, prospective, open-label, uncontrolled Phase 3b study is ongoing. For this marketing application, it provides supportive safety data and limited efficacy data (i.e., a listing of any bleeding events reported at the time of data cutoff). The final results will assess the predictive ability of the surrogate endpoint in Study 2001 (trough Factor XIII activity levels) in preventing spontaneous bleeding episodes.

Male or female subjects of any age with congenital Factor XIII deficiency were eligible. Subjects who completed Study 2002 were offered enrollment, as well as subjects enrolled in Study 5986 and those not currently enrolled in any study. Approximately 40 will be enrolled to obtain 32 evaluable (per protocol) subjects;

Doses are guided by the individual subject's Factor XIII activity levels, with the objective of dosing every 28 days to maintain a trough Factor XIII activity level of 5

to 20%. Initial doses were 40 U/kg, except for those subjects previously in Study 2002 whose dose was adjusted from 40 U/kg based on trough FXIII activity levels achieved in that study.

Efficacy endpoints are the frequency and severity of bleeding episodes following prophylactic treatment. The primary endpoint is the incidence density through Week 52 of spontaneous bleeding events requiring administration of a Factor XIII-containing product to treat the bleeding event. Secondary efficacy in the treatment of acute bleeding events, and during and after surgical procedures, is assessed using ratings of hemostatic efficacy.

Efficacy measurements include:

- *Bleeding event severity* is categorized from Grade 1 to 5 by the investigator using the NCI CTCAE.
- *Bleeding event type* is rated as spontaneous, traumatic, associated with surgery, or “other”.
- *Inhibitor antibodies* are obtained as soon as possible following any bleeding event of \geq Grade 2 intensity using the NCI CTCAE.
- *Hemostatic efficacy following treatment of acute bleeding events* is assessed with the primary rating of successful or unsuccessful.
- *Overall hemostatic efficacy following treatment for scheduled surgery* is assessed with the primary rating of successful or unsuccessful.

The study will also investigate the long-term PK and safety of the study treatment. Safety assessments include AEs, laboratory safety parameters, virology testing, Factor XIII antibody testing, vital signs, and physical examination.

The study design includes a four week screening period and a 12 month treatment period, yielding an individual subject study duration of approximately 13 months. Upon completion of this study, subjects were offered to continue in the open enrollment study (Study 3002).

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

Enrollment is complete with 43 subjects enrolled; 41 were treated with the study treatment and two were screening failures. Two subjects have completed the study and 39 subjects are ongoing in the study.

The safety population consists of all subjects who received at least one dose of study treatment. The efficacy population consists of all subjects from the safety population who were assessed for efficacy at baseline and had at least one follow-up FXIII activity trough level. The per-protocol efficacy population consists of all subjects in the safety population who do not have major protocol violations and completed at least 24 weeks of scheduled treatment.

Among the 41 subjects in the safety population, 25 (61.0%) are male. Eighteen (43.9%) are Caucasian, ten (24.4%) are Hispanic, seven are Black/African-American, four Asian and two “other”. The mean age at screening is 20.1 (11.20 SD) years, with 18 (43.9%) subjects < 16 years and 23 subjects 16-64 years.

The mean age of diagnosis is 5.4 years. All subjects except one had been treated with FXIII in the six months prior to entering this study.

3.1.2.3 Statistical Methods

The primary endpoint will be calculated as the total number of spontaneous bleeding events requiring treatment observed divided by the accrued exposure time (person-years). However, the sponsor provided in the interim report contained in this submission only an overall summary of spontaneous bleeding episodes requiring treatment for the efficacy and per-protocol efficacy populations.

All summary tables provided by the sponsor for this analysis (a subset of those to be provided in the full analysis) were performed on the safety population. Descriptive statistics (mean, SD, median, range, quartiles) were planned for continuous variables, and frequency and percentage for categorical variables.

3.1.2.4 Results and Conclusions

To date, a total of 364 doses (9098 exposure days) have been administered. Three subjects have experienced a total of 6 bleeding events (Table 2). One subject experienced two rectal bleeding events, another subject experienced two nose bleeds and a bruise on the right finger, and a third subject experienced a head laceration. In addition, three bleeding events not yet included in the database were reported to CSLB for three other subjects.

Table 2: Study 3001 Bleeding Events

Event	Severity (CTCAE 1-5)	Event Type	Inhibitor Antibodies	Primary Hemostatic Efficacy¹	Secondary Hemostatic Efficacy²
Rectal bleeding #1	1	spontaneous	n/a	successful	excellent
Rectal bleeding #2	1	spontaneous	n/a	successful	excellent
Nose bleed #1	1	spontaneous	n/a	successful	excellent
Nose bleed #2	1	spontaneous	n/a	successful	excellent
Right finger bruise	1	traumatic	n/a	successful	excellent
Head laceration	2	traumatic	n/a	successful	excellent

¹ successful or unsuccessful

² excellent, good, poor or none

None of the events required administration of FXIII. Therefore, the incidence density at this time of spontaneous bleeding events requiring administration of FXIII to treat the bleeding event is zero.

3.1.3 Study 3002 (Supporting Study)

Objectives:

- to allow provision of study medication to US subjects until the study treatment becomes commercially available in the US.
- to collect additional long-term safety data.

3.1.3.1 Study Design and Endpoints

This multicenter, prospective, open-label, uncontrolled Phase 3b study is ongoing. This open enrollment study is offered to provide prophylactic treatment with FXIII treatment for all subjects with congenital FXIII deficiency. These subjects would not otherwise have access to FXIII concentrate. Male or female subjects of any age with congenital Factor XIII deficiency were eligible.

Subjects will have a dosing visit every 28 days; FXIII activity level will be measured every 24 weeks. Subjects who did not complete Study 2002 or receive at least three doses of study treatment in Study 3001, as well as subjects enrolled directly from Study 5986, receive study treatment at a dose of 40U/kg. For all other subjects and all doses at baseline, the dose is guided by the individual subject's most recent pre-infusion trough Factor XIII activity levels, with the objective of dosing every 28 days to maintain a trough Factor XIII activity level of approximately 5-20%.

Efficacy endpoints for the study are incidence and frequency of bleeding events. Safety is assessed at each visit based on the following variables: AEs, FXIII activity level and antibody testing. Serum chemistries and hematology are also assessed at specific time points.

Enrollment remains open, with interim data provided in this submission. Based on the number of FXIII deficient patients requiring prophylactic treatment identified in the US, the sponsor estimates that approximately 50-100 subjects may be enrolled in the study. The expected duration of treatment is up to two years or until the study treatment becomes commercially available in the US.

3.1.3.2 Patient Disposition, Demographic and Baseline Characteristics

Twenty-four subjects (54.2% females) have enrolled and are ongoing. The majority of subjects are Caucasian (70.8%) and between 16 and 65 years at screening (54.2%), with 19.0 years the mean age at screening.

The safety population will consist of all subjects who received at least one dose of study treatment during the study. All safety analyses will be performed on the safety population.

3.1.3.3 Statistical Methods

All AEs are coded using MedDRA. Laboratory parameters will be summarized descriptively.

3.1.3.4 Results and Conclusions

To date, 80 infusions (1605 exposure days) have been given; the majority of subjects (66.7%) have received one infusion. One subject had two bleeding events: increase in bruising and large hematomas (an SAE), and a small cut/abrasion on the nose. No infusions for bleeding events have occurred.

3.1.4 Study 5001 (Supporting Study)

Primary objectives:

Safety and tolerability

- Immediate tolerability
- Suspected adverse drug reactions
- Incidence of inhibitor development
- Viral safety (where appropriate follow-up is guaranteed)

Pharmacokinetics/efficacy

- Reversal of coagulation factor deficit (increment in activity)
- Supporting clinical management of an acute hemostatic imbalance (bleeding)
- Incidence of spontaneously induced bleeding episodes

3.1.4.1 Study Design and Endpoints

This multicenter, prospective, open-label, non-controlled post-marketing surveillance (Phase 4) study is complete. As such, prospective data was collected on the routine management of patients with congenital FXIII deficiency, including their follow-up. The number of subjects was not based on a statistical rationale but rather as that determined by available patients.

Subjects could receive prophylactic treatment and/or on demand treatment. The amount and frequency of study treatment was based on clinical efficacy. It was administered at approximately 10 U/kg every four weeks for hemorrhage prophylaxis, up to 35 U/kg immediately before surgical operations and approximately 10 U/kg for the following five days, and 10-20 U/kg daily in case of severe hemorrhage and extensive hematomas.

Efficacy was assessed as increment in FXIII activity and, secondarily, incidence of bleeding/thrombotic events, differentiating between prophylactic and therapeutic treatment regimens. In addition, the investigator used a four-grade scale (excellent, good, moderate, none) to judge hemostatic efficacy.

Male or female subjects of any age with congenital FXIII deficiency were eligible. Patients with known relevant antibodies/inhibitors to FXIII were not eligible. Patients could be either previously treated or untreated. At least ten patients treated for at least two years with Aventis Behring product were planned to be included.

3.1.4.2 Patient Disposition, Demographic and Baseline Characteristics

No patient discontinued the study early. The mean cumulative duration in the study was 677 days and ranged from 357 to 780 days.

Fourteen of the 19 subjects enrolled were male. The age ranged from < one month to 47 years. Fifteen subjects were Caucasian, two Asian, and two “other”.

The median value of residual FXIII activity at time of enrollment was 1.0%. Two subjects had been treated with FXIII product exclusively from Aventis Behring, while the other 17 subjects had also received other products. At the first visit, no subject had inhibitors against FXIII. Eight subjects had a total of 12 hemorrhages reported within the last year prior to starting the study.

3.1.4.3 Statistical Methods

Due to the open and non-controlled design, descriptive methods were planned for the various efficacy/safety parameters. All analyses were performed on a per-protocol basis (i.e., for subjects with documented baseline and follow-up information).

3.1.4.4 Results and Conclusions

Table 3 shows the bleeding events reported during the study. No thrombotic events were reported.

Table 3: Study 5001 Bleeding Events

Treatment Regimen	Subjects with no events	Subjects with events	
		<i># of subjects</i>	<i># of events</i>
Prophylaxis	8	4	≥19
On demand	0	3	8
Both	1	3	16
Total	9	10	≥43

The data show that over half (52.6%: 10 out of 19) of the subjects had bleeding events. None of the events that occurred in subjects on prophylactic treatment were treated with FXIII Concentrate (Human).

3.1.5 Study 5986 (Supporting Study)

Objectives: determine the safety, efficacy, and PK of the study treatment.

3.1.5.1 Study Design and Endpoints

This multicenter, prospective, open-label Phase 2/3 study is ongoing. This study is conducted under IND (b)(4). Male or female subjects of any age with congenital FXIII deficiency are eligible. A maximum of 80 subjects are planned with 72 subjects enrolled. This sample size is not based on statistical considerations; 80 subjects would represent 60-80% of all reported cases of severe FXIII deficiency in the US.

The first dose of study treatment is administered as 20 U/kg, with subsequent doses of 10-20 U/kg once every four weeks until the subject's PK results were available, at which time the dose is tailored to the subject's PK profile.

The efficacy endpoint is all bleeding episodes that require infusion with study treatment. Safety endpoints include AEs, laboratory assessments, vital signs, and physical examination results.

3.1.5.2 Patient Disposition, Demographic and Baseline Characteristics

Of the 72 subjects enrolled, 59 (81.9%) had completed at least one year of the study and 13 subjects were discontinued from the study before one year. A total of 2745 infusions were administered, with a mean of 35 infusions per subject.

Among the 72 subjects, 66.7% were male and 47.2% were Caucasian. At screening, the mean age was 17.8 years and 51.0% were 16 to 64 years of age.

The safety population was defined as all subjects who received at least one dose of the study treatment and was the only population analyzed for this study.

3.1.5.3 Statistical Methods

Tabular data summaries will be presented to provide an overview of selected study findings. Descriptive statistics (n, mean, SD, median, range, quartiles) were planned for continuous variables, and frequency and percentage for categorical variables.

Only the bleeding narratives are included in this market application; the efficacy data are summarized but not considered supportive to the BLA as there was no prospective description of efficacy criteria in this study protocol. Specifically, the number of bleeds requiring infusions will be summarized, along with the response to treatment, and included in the data listings. All other infusion data including prophylaxis treatments and data collected during and after surgical procedures will only be included in the data listings.

3.1.5.4 Results and Conclusions

Of the 72 enrolled subjects, 22 subjects (30.6%) had 34 bleeding events that required administration of study treatment. Only one severe bleeding event (intracranial hemorrhage) was reported.

Eleven subjects had a single bleeding event, and 11 subjects had multiple bleeding events (one subject had three, and 10 subjects had two each). The anatomic location of bleeding events included muscular and joint (five each) and central nervous system and GI (two each). The location of 20 events was reported as "other".

3.2 Evaluation of Safety

The safety program consists of 12 clinical studies: the five efficacy studies discussed in Section 3.1 plus seven additional supportive studies in various populations: one in

healthy volunteers (**Study 1003**), four in congenital FXIII deficiency (**Studies 7D-101PK, 7MN-101PK, 7MN-101PK Extension, 201**), and two in -----(b)(4)----- (**Studies 301CL, 302CL**). The safety data was not standardized in the supporting studies as most of them pre-date the GCP and ICH guidelines. A synopsis of the seven additional studies follows.

3.2.1 Safety-only Studies

The following studies provide only safety data to the submission.

3.2.1.1 Study 1003

This uncontrolled, open-label, prospective phase 1 study was conducted in 20 male Caucasian healthy volunteers aged 18.9 to 34.9 years. The study was designed to evaluate PK parameters and safety of the FXIII Concentrate (Human) with special reference to viral markers. Each subject received a single bolus infusion (30 U/kg) of FXIII Concentrate (Human).

3.2.1.2 Study 7D-101PK

(b)(4)

3.2.1.3 Study 7MN-101PK

(b)(4)

3.2.1.4 Study 7MN-101PK Extension

This single center, uncontrolled, open, prospective extension study was conducted in two female subjects (ages 30 and 53) from the original study. The study was designed to determine the effect of repeated dosing on PK and to evaluate the efficacy and safety of plasma-derived FXIII Concentrate (Human) for long-term therapy of congenital FXIII deficiency. The subjects were to receive six to nine single doses (30 U/kg) when FXIII activity dropped below 10%; one subject received eight doses and the other received nine.

3.2.1.5 Study 201

This open-label uncontrolled study was conducted in four subjects (age range 26-43 years; three male) with congenital FXIII deficiency. The objective was to investigate the safety and *in vivo* recovery and half-life of FXIII Concentrate (Human) after a single administration in order to gain usage experience as a replacement therapy drug for congenital FXIII-deficient subjects. The average dose was 17.7 U/kg.

3.2.1.6 Study 301CL

(b)(4)

3.2.1.7 Study 302CL

(b)(4)

3.2.2 Safety Assessments

Safety assessments were made in all 12 clinical studies. These assessments included AEs, laboratory tests, vital signs, physical examinations, and viral safety (although not all assessments were made in all studies). In these 12 studies, a total of 3642 doses of FXIII Concentrate (Human) were administered, 3282 of which were administered to subjects with congenital FXIII deficiency. A total of 218 unique subjects received at least one dose of FXIII Concentrate (Human) in the 12 clinical studies (35 of these subjects did *not* have congenital FXIII deficiency).

In the FXIII Concentrate (Human) clinical program, one thromboembolic event was reported in a subject who did *not* have congenital FXIII deficiency and received a total dose of FXIII Concentrate (Human) that was over five times the normal dose for congenital deficiency. One subject experienced an AE of hypersensitivity, and ten additional subjects experienced symptoms of hypersensitivity. One subject (Study 3002) demonstrated clinical and laboratory findings consistent with transient FXIII inhibitor development; this was a study treatment related SAE. Measurements for FXIII inhibitors were not performed for Studies 1003, 301CL, and 302CL.

The incidence of treatment-emergent AEs and SAEs for each study's safety population is shown in Table 4. The only deaths occurred in Study 5986 and were not related to study treatment.

Table 4: Treatment-Emergent AEs

Study #	N	Type of Treatment-Emergent AE n (%)				
		at least one AE	at least one possibly related AE	at least one SAE	at least one possibly related SAE	Deaths
2002	14	8 (57.1)	2 (14.3)	0	0	0
3001	41	12 (29.3)	1 (2.4)	1 (2.4)	0	0
3002	24	12 (50.0)	1 (4.2)	1 (4.2)	1 (4.2)	0
5001	19	2 (10.5)	1 (5.3)	1 (5.3)	0	0
5986	72	40 (55.6)	3 (4.2)	8 (11.1)	0	3 (4.2)
1003	20	8 (40.0)	4 (20.0)	0	0	0
7D-101PK	1	1 (100.0)	0	0	0	0
7MN-101PK	13	6 (46.2)	4 (30.8)	0	0	0
7MN-101PK (Extension)	2	2 (100.0)	0	0	0	0
201	4	0	0	0	0	0
301CL	28	3 (10.7)	2 (7.1)	0	0	0
302CL	33	8 (24.2)	2 (6.1)	1 (3.0)	1 (3.0)	0

3.3 Gender, Race, Age and Other Special/Subgroup Populations

In the pivotal study (Study 2002), half of the 14 subjects in the safety population were female (50.0%). Approximately one-third (35.7%) each were Caucasian and Black/African American; two subjects (14.3%) each were Asian and Hispanic. At screening, the mean age was 24.0 (12.55 SD) years; all subjects were < 65 years of age, and 5 (35.7%) were < 16 years.

In the confirmatory study (Study 3001), 25 (61.0%) of the 41 subjects in the safety population are male. Eighteen (43.9%) are Caucasian, ten (24.4%) are Hispanic, seven are Black/African-American, four Asian and two "other". The mean age at screening is 20.1 (11.20 SD) years, with 18 (43.9%) subjects < 16 years and 23 subjects < 65 years.

No inferential statistics were performed due to the limited number of events.

3.3.1 Efficacy

None of the subjects in the completed pivotal study had a bleeding event; therefore the incidence density of subjects requiring treatment with FXIII for a bleeding event is zero.

To date, three subjects have had six bleeding events (four spontaneous) in the confirmatory study. All three subjects are male, one (33.3%) is < 16 years of age and Hispanic, and two (66.7%) are \geq 16 years old and Caucasian. None of the four spontaneous events required administration of FXIII. Therefore, the incidence density at this time of spontaneous bleeding events requiring administration of FXIII to treat the bleeding event is zero.

3.3.2 Safety

In the pivotal study, four of the five (80%) subjects < 16 years of age and four of the nine (44.4%) subjects \geq 16 years of age had at least one treatment-emergent AE. More females (five of seven [71.4%]) than males (three of seven [42.9%]) experienced \geq 1 treatment-emergent AE. One of five (20%) Caucasians, four of five (80%) Black/African Americans, one (50%) Hispanic, and both Oriental/Asians had at least one treatment-emergent AE.

To date, the only treatment-emergent AE experienced in the confirmatory study by >1 subject in any gender or age subgroup has been abrasions in 2 male (one Hispanic, one Oriental/Asian) subjects (8.0%). No treatment-emergent AEs have been experienced by >1 subject in any racial subgroup. Male subjects experienced a higher percentage of treatment-emergent AEs compared to female subjects (nine of 25 [36.0%] vs. three of 16 [18.8%], respectively). A similar percentage of subjects <16 years of age and between 16 and <65 years of age experienced treatment-emergent AEs (five of 18 [27.8%] and seven of 23 [30.4%], respectively) and a similar percentage of Caucasian and Hispanic subjects experienced at least 1 treatment-emergent AE (four of 18 [22.2%] and three of ten [30.0%], respectively). Of note, all 4 Oriental/Asian subjects experienced treatment-emergent AEs and no Black/African Americans experienced a treatment-emergent AE.

One subject (Study 3002) who had a study treatment related SAE (transient FXIII inhibitor development) is a 26 year old Caucasian female; the other is a 74 year old male of unknown race. The three deaths (Study 5986) were all Caucasian male \geq 16 years of age.

4. SUMMARY AND CONCLUSIONS

4.1 Efficacy Summary

This marketing application contains one pivotal and four supporting efficacy studies. The pivotal study is a PK study with a surrogate clinical endpoint. The efficacy variable measured in the pivotal study is the achievement of a trough FXIII activity level of $\geq 5\%$, which is believed to predict the hemostatic efficacy of the FXIII Concentrate (Human) replacement therapy in preventing spontaneous bleeding episodes. A confirmatory study of the surrogate endpoint was started prior to the marketing submission; the primary endpoint is the incidence density through Week 52 of spontaneous bleeding events requiring administration of a Factor XIII-containing product to treat the bleeding event. The results from this study, the pivotal study, and three other studies support the clinical development program.

Table 5 summarizes the bleeding event information (not all spontaneous events) to date for those subjects in the efficacy studies receiving prophylactic treatment. As no bleeding events in the confirmatory study required treatment, the current incidence density is zero.

Table 5: Summary of Bleeding Events

Study	n	# subjects with events (%)	# events	# events requiring FXIII treatment
2002 (pivotal study)	14	0 (0.0)	0	0
3001 (confirmatory study)	41	3 (7.3)	6*	0
3002	24	1 (4.2)	2	0
5001	12	4 (33.3)	≥ 19	0
5896	72	≥ 22 (30.6)	≥ 34	34

* Four spontaneous; 2 traumatic

4.2 Safety Summary

The safety program consists of 12 clinical studies: the five efficacy studies plus seven additional supportive studies in various populations: one in healthy volunteers, four in congenital FXIII deficiency, and two in -----(b)(4)-----. In these 12 studies, a total of approximately 3930 doses of FXIII Concentrate (Human) were administered, 3570 of which were administered to subjects with congenital FXIII deficiency. A total of 187 unique subjects received at least one dose of FXIII Concentrate (Human) in the 12 clinical studies (35 of these subjects did *not* have congenital FXIII deficiency).

One thromboembolic event was reported in a subject who did *not* have congenital FXIII deficiency and received a total dose of FXIII Concentrate (Human) that was over five times the normal dose for congenital deficiency. One subject experienced an AE of hypersensitivity, and ten additional subjects experienced symptoms of hypersensitivity. Nine studies performed FXIII inhibitor development testing. One subject demonstrated

clinical and laboratory findings consistent with transient FXIII inhibitor development; this was a study treatment related SAE.

4.3 Conclusions and Recommendations

The primary efficacy endpoint is a PK endpoint. The surrogate endpoint in the ongoing confirmatory study (incidence density through Week 52 of spontaneous bleeding events requiring administration of a Factor XIII-containing product to treat the bleeding event) currently shows an incidence of zero. Only one of the efficacy studies on the clinical development program has subjects (on prophylactic treatment) with FXIII treatment of bleeding events. One out of 132 (0.76%) unique subjects in nine clinical studies demonstrated transient FXIII inhibitor development.

This reviewer has no objections to the approval of FXIII Concentrate (Human).

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