



STATISTICAL REVIEW AND EVALUATION BLA (MID-CYCLE 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.

This statistical review covers the efficacy study results for the mid-cycle review memo. Review of the safety studies is on-going.

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 (A₂B₂) plasma protein and a homodimeric (A₂) 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 (A₂) 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	27 (ongoing); max 40	Long-term efficacy, safety, PK (Phase 3b; post-marketing)
3002	Prospective, open-label, multicenter, single-arm	Congenital FXIII deficiency	3 (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
7D-101PK	Prospective, randomized, active-controlled crossover	Congenital FXIII deficiency	1	BE/PK/PD/safety (pilot study)
7MN-101PK	Prospective, randomized, active-controlled crossover	Congenital FXIII deficiency	13	BE/PK/PD/safety
7MN-101PK	Prospective, open-label, uncontrolled	Congenital FXIII deficiency	2	PK/PD/safety (long-term follow-up)
201	Open-label,	Congenital	4	PK/PD/safety

<i>Study #</i>	<i>Design</i>	<i>Population</i>	<i>N</i>	<i>Purpose</i>
<i>Efficacy Studies</i>				
	uncontrolled	FXIII deficiency		
301CL	Prospective, randomized, placebo-controlled, multicenter, two- arm	----(b)(4)--- -----	28	Safety
302CL	Prospective, randomized, placebo-controlled, multicenter, three-arm	----(b)(4)--- -----	33	Safety

2.2 Data Sources

All data sources are included in the sponsor’s eCTD submission located in the FDA/CBER Electronic Document Room (EDR) at the following link:

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

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 Factor XIII 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 Factor XIII activity level of $\geq 5\%$. This surrogate efficacy endpoint of trough Factor XIII activity levels is believed to predict the hemostatic efficacy of the Factor XIII 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:

1. evaluate the association between Factor XIII activity peak and trough levels and the incidence of spontaneous bleeding events requiring treatment
2. collect and evaluate additional long-term PK data
3. evaluate hemostatic efficiency in treatment of acute bleeding events and for surgery prophylaxis
4. 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

As of this interim report, 31 subjects were screened and 27 enrolled. Each of the enrolled subjects is 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 have no major protocol violations and completed at least 24 weeks of scheduled treatment.

Among the 27 subjects in the safety population, 14 (51.9%) are female. Almost half (48.1%) are Caucasian, six (22.2%) are Hispanic, five are Black/African-American, two Asian and one “other”. The mean age at screening is 17.8 years, with 13 subjects < 16 years and 14 subjects 16 -64 years.

The mean age of diagnosis is 4.4 years. All subjects 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 interim 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

A total of 81 infusions have been administered to date. One subject had two bleeding events: nose bleed (spontaneous) and contusion of finger (trauma). Neither required administration of FXIII. Therefore, the incidence density at the time of this interim report of spontaneous bleeding events requiring administration of FXIII to treat the bleeding event is zero. Both events were rated successful for hemostatic efficacy and no inhibitor antibodies were measured as both were Grade 1 events.

3.1.3 Study 3002 (Supporting Study)

Objectives:

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

3.1.3.1 Study Design and Endpoints

This multicenter, prospective, open-label, uncontrolled Phase3b 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

Three subjects (two males) have enrolled and are ongoing. All are Caucasian with 11.7 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, no bleeding events have occurred during the study.

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 Factor XIII 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 will be 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 2 shows the bleeding events reported during the study. No thrombotic events were reported.

Table 2: Study 5001 Bleeding Events

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

The most frequently observed bleeding events were hemorrhages into soft tissue and the muscular system in a total of 5 out of 19 subjects. The data show that almost half (47.4%: 9 out of 19) of the subjects did not have bleeding events.

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 Factor XIII 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, four in congenital Factor XIII deficiency, and two in -----(b)(4)-----). In these 12 studies, a total of 3284 dose of Factor XIII Concentrate (Human) were administered, 2924 of which were administered to subjects with congenital Factor XIII deficiency. In addition to the SAS data sets provided for three of the efficacy studies, a safety data set was provided for efficacy Study 5986. A review of the safety program is ongoing.

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

A complete review of the subgroup populations is ongoing.

3.3.1 Study 2002

As no bleeding events occurred in the currently available data set, no subgroup efficacy analyses were performed.

3.3.2 Study 3001

Due to the limited number of bleeding events (n=2) at the time of this interim summary, subgroup efficacy analyses were not performed.

3.3.3 Study 3002

As no bleeding events occurred in the currently available data set, no subgroup efficacy analyses were performed.

3.3.4 Study 5986

The majority of bleeding events (24/34) occurred in subjects <20 years of age.

4. SUMMARY AND CONCLUSIONS

This marking application contains one pivotal and four supporting efficacy studies. Table 3 summarizes the bleeding events across all five efficacy studies. This statistical review memo is for the mid-cycle assessment for the biologic license application under STN 125385. Prior to the completion of the post-marketing study (study 3001), I expect OBRR will provide the criteria for defining success of the efficacy endpoint.

Table 3: Summary of Bleeding Events

Study	# events	# subjects with events	# subjects enrolled
2002	0	0	14
3001	2	1	27
3002	0	0	3
5001	43	10	19

Study	# events	# subjects with events	# subjects enrolled
5896	34	22	72

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