

STN (ref IND): 125385/0 (ref IND 13882)

PRIORITY DESIGNATION: Yes

APPLICANT: CSL Behring

PRODUCT: Factor XIII Concentrate (Human)

INDICATION: Routine prophylactic treatment of congenital FXIII deficiency

ROUTE OF ADMINISTRATION: Intravenous use only

DATE SUBMITTED: August 18, 2010

ADD: February 17, 2011

REVIEWER: Daniela J. Vanco, M.D.

SUBJECT: Clinical Review

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1 RECOMMENDATION ON REGULATORY ACTION

The licensure of Corifact™ for routine prophylactic treatment of congenital Factor XIII (FXIII) deficiency is recommended. The effectiveness of Corifact is based on maintaining a trough FXIII activity level of approximately 5% to 20% as the surrogate endpoint. A post-marketing study to validate the clinical benefit of hemostasis by achieving pre-specified plasma trough levels is currently ongoing. Evidence that Factor XIII levels are likely to predict clinical benefit in this rare factor deficiency is supported by almost 20-year-long clinical use of FXIII Concentrate (Human), which has been approved and marketed in Europe as Fibrogammin® P. In addition, data obtained under US IND (b)(4) provide supportive evidence of effectiveness of Corifact™ in congenital FXIII deficient patients. The safety of Corifact for the intended indication is supported by data obtained from 12 clinical studies.

2 EXECUTIVE SUMMARY

CSL Behring GmbH (CSLB), Applicant, submitted the BLA for Factor XIII Concentrate (Human) under the Accelerated Approval regulation [21 CFR 314.510] using Factor (F) XIII activity trough levels as the surrogate endpoint. As mandated by the Accelerated Approval regulation, a post-marketing study to correlate the achieved plasma FXIII trough levels to clinical benefit is currently ongoing. The product, with the proprietary name of Corifact™, is indicated for routine prophylactic treatment of congenital FXIII deficiency.

Corifact has shown a favorable safety profile. Clinical efficacy of the product, however; is to be determined in a post-marketing Phase 4 Study, which is designed to show the correlation of the trough FXIII levels (a surrogate marker) and the clinical outcomes during treatment of bleeding episodes in patients with congenital FXIII deficiency.

Corifact is a lyophilized concentrate for reconstitution, administered intravenously at the initial dose of 40 International Units (IU)/kg body weight.

Subsequent Dosing should be guided by the most recent trough FXIII activity level, with dosing every 28 days (4 weeks) to maintain a trough FXIII activity level of approximately 5% to 20%. Recommended dosing adjustments of ± 5 IU/kg should be based on trough FXIII activity levels of $<5\%$ or $>20\%$ as outlined in Table 1, and the patient's clinical condition. Dosing may need to be adjusted following a bleeding event.

FXIII Activity Trough Level (%)	Dosage Change
One trough level of $<5\%$	Increase by 5 IU/kg
Trough level of 5% to 20%	No change
Two trough levels of $>20\%$	Decrease by 5 IU/kg
One trough level of $>25\%$	Decrease by 5 IU/kg

The injection rate should not exceed 4ml per minute.

Included in the BLA submission is a Pivotal PK efficacy Study BI71023_2002, which evaluated trough FXIII levels as a surrogate endpoint to demonstrate hemostatic efficacy and safety to support approval of Corifact, Factor XIII Concentrate (Human), for routine prophylactic treatment of congenital FXIII deficiency. In addition to the Pivotal Study, eleven supportive efficacy and/or safety studies, are included in this submission.

Twelve studies contributing to the overall clinical development of Corifact, included 187 subjects, 90 of whom were subjects < 16 years old. In the pivotal study, the efficacy population consisted of 13 patients and safety population of 14 patients, of whom 5 were subjects < 16 years old.

The pivotal study BI71023_2002 to support the approval was conducted as part of the clinical development program to establish the steady-state pharmacokinetics (PK) of Factor XIII Concentrate (Human). Based on historic evidence, maintaining a trough Factor XIII level of $\geq 5\%$ was selected as the surrogate endpoint for hemostatic efficacy of the proposed Factor XIII replacement therapy. This was an open-label, single-arm, multi-center, PK study of CorifactTM 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 as a bolus intravenous (IV) injection at 250 U/minute for a total of 3 doses over 12 weeks. There were 13 subjects in the study (6 males and 7 females). 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. As supplementary analyses, the PK of Factor XIII was assessed on the basis of measurements of Factor XIII activity using the -----(b)(4)----- and the Berichrom assay amended for background signal. Pharmacokinetic parameters were assessed for Factor XIII activity using a non-compartmental model.

Total of 3,930 doses of Factor XIII Concentrate (Human) have been administered in the 12 clinical trials included in this BLA application. Of the 3930 doses of Factor XIII Concentrate (Human), 3,590 doses were administered to subjects with rare congenital Factor XIII deficiency.

There were no deaths, life-threatening events or adverse events that led to study discontinuation in the pivotal study to support this BLA application. Eight subjects in the study experienced treatment-emergent adverse events (TEAE) of mild to moderate severity (5 subjects experienced infections, injury, bruising and contusion, ecchymosis, borderline diabetes), three subjects within 24 hours, three subjects within 72 hours of infusion. No episodes of thrombo-embolism or viral transmission were identified during the study. The two occurrences of laboratory increases (thrombin-antithrombin III complex increased and prothrombin increased and fibrin D-dimer increased) were not associated with any clinical signs of thrombo-embolism, and were possibly related. One subject experienced a mild rash on Day 65 that was considered unrelated to study product and was ongoing.

The safety data from the ongoing post-marketing study had a collection cut-off date on February 15, 2010. This data was submitted to the BLA in November 2010. An SAE consistent with a neutralizing inhibitor to Factor XIII was reported in a 26-year old subject with congenital FXIII deficiency. The patient's FXIII levels returned to baseline after plasmapheresis. The patient was re-exposed to Corifact™ and has not reported any breakthrough bleeding.

In a study of -----b(4)----- (302 CL), consisting of 33 subjects, one subject experienced a myocardial infarction (MI). This subject was a 74-year old male with a history of coronary heart disease and suffered acute myocardial infarction one day after the last study drug infusion. The subject was not Factor XIII deficient and received five times the dose given for congenital deficiency patients.

In the post-marketing safety surveillance, an MI was reported seven days after administration of Fibrogamin P (trade name of Corifact™ in EU) in a congenital deficient patient. The causality was assessed as possible. Two other cases of thrombo-embolic events were reported in patients with no known FXIII deficiency. The causality was assessed as possible.

Under the accelerated approval program, the Applicant is currently conducting a Phase 4 study (Study No BI71023_3001) to verify the clinical benefit by showing a correlation between trough levels of FXIII (5% to 20%) and clinical efficacy, and also by comparing the incidence of bleeding with treatment to historical control without treatment. This is a multi-center, prospective, open-label study that will include 41 subjects. The efficacy endpoints are the frequency of bleeding episodes following prophylactic treatment. The sample size calculation is designed to detect a 50% reduction in the incidence of breakthrough bleeding with treatment compared to the historical rate without treatment. This study is ongoing (since August 2009) and the projected completion date is April 17, 2011. The final study report will be submitted by December 31, 2011.

This submission did not trigger PREA because of Orphan Drug status.

OBRR reviewed information from this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure is not needed for the following reasons (FDAAA [HR 3580-138 SEC. 918: REFERRAL TO ADVISORY COMMITTEE]):

- The mechanisms of action of Factor XIII Concentrate (Human) and its role in blood coagulation are well understood.
- The mechanism of action and safety profile of the product is fully understood, as it has been used widely outside the U.S. since 1993.
- The review of the clinical data does not raise any safety concerns with regard to thrombogenicity and immunogenicity.

- BPAC discussion of this application is unlikely to change the outcome of the review of this file from a regulatory standpoint.

3 REVIEW RESPONSIBILITIES

Product and Chairperson:	Ze Peng, Ph.D.
Medical:	Daniela J. Vanco, M.D.
Statistician:	Renee Rees, Ph.D.
RPM:	Nanette Cagungun
BIMO:	Dennis Cato
DMPQ	Martha O'Lone & Jennifer Schmidt
APLB:	Michael Brony
OBE	Alan Ou
Pharmaco-Toxicology:	La'Nissa Brown-Baker, Ph.D.
Clinical Pharmacology:	Iftekhhar Mahmood, Ph.D.

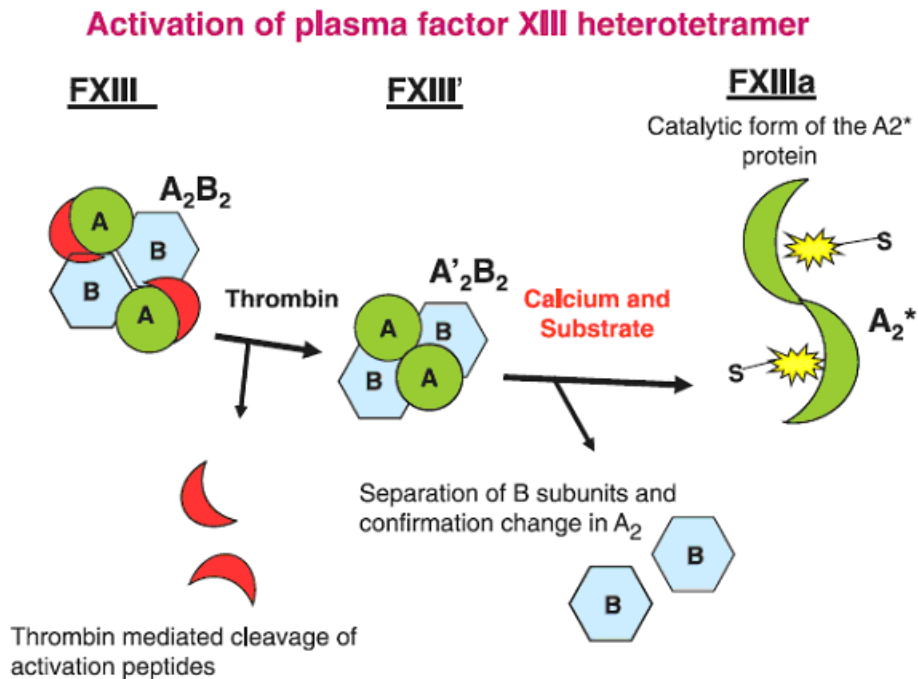
4 INTRODUCTION AND REGULATORY BACKGROUND

4.1 Product Information

Corifact is a purified pasteurized concentrate of blood coagulation Factor XIII (containing both subunits, A and B), produced by CSL Behring GmbH Marburg, Germany. FXIII Concentrate (Human) is a lyophilized plasma protein product prepared from US source human plasma for fractionation and is manufactured in the CSL's Marburg, Germany facility. This product was first licensed under the trade name Fibrogammin P in 1993 in the United Kingdom. Currently, the product is licensed in 14 other countries, not in the US.

In plasma, FXIII pro – enzyme circulates in form of a tetramer composed of two catalytic A subunits bound to two carrier B subunits (A₂B₂) (Lorand et. al 1980). Intracellularly, FXIII is found as a homodimer of the two A subunits (A₂) (Schwartz et al 1973). The A subunit constitutes the catalytic moiety and the B subunit is thought to play a role in stabilization of the A subunit. On activation by thrombin and Ca²⁺, the A and B subunits dissociate. The A subunit is then cleaved to produce the catalytically active form of the protein, A₂* (Takagi&Doolittle 1974). A₂* catalyzes the Ca²⁺ - dependent formation of glutamyl-lysine bonds between fibrin and other protein molecules.

Figure 1 Activation of plasma factor XIII and **Figure 2.** Factor XIII A: gene (F13A) and protein structure (1192 L. HSIEH and D. NUGENT)



Congenital FXIII deficiency is a rare bleeding disorder. The estimated incidence in US is 1 in 3-5 million births. This deficiency is an autosomal recessive disorder. Heterozygous individuals are asymptomatic. Umbilical cord bleeding is the most common manifestation, occurring in up to 80% of patients. The incidence of intracranial hemorrhage has been reported in 25-60% of patients, a frequency much higher than that seen in any other congenital bleeding disorder, including the most severe hemophiliac and type 3 von Willebrand Disease. The Factor XIII Registry Database includes 104 patients out of 88 families from 14 countries. The incidence of intra-cranial bleeding in this group of patients is 34%. There is a very high rate of recurrence in patients who do not receive appropriate prophylaxis. Mucous membrane bleeding and surgical bleeding have also been observed, but are often delayed, probably due to poor clot stability. Rate of miscarriage is very high in women with the disorder.

Current treatment and prophylaxis options include cryoprecipitate, fresh frozen plasma (FFP), and preparations of plasma-derived FXIII concentrates.

Rationale for the use of Factor XIII in Congenital Deficiency of FXIII:

Factor XIII is a plasma pro-enzyme that promotes the cross-linking of fibrin during blood coagulation. FXIII is converted by calcium and thrombin into the active enzyme FXIIIa, 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. FXIII has a long circulating half-life (10 days) and full hemostatic activity even at low concentrations, making it particularly suitable for routine prophylactic replacement therapy.

4.2 Regulatory Background

The following summarizes the regulatory chronology of this BLA:

On January 16, 1985 FDA granted orphan designation (Application No. 84-0044) to FXIII Concentrate for the treatment of congenital factor XIII deficiency.

On July 12, 2007 at a CBER Pre-BLA meeting, the following points were discussed:

- PK study acceptability as pivotal.
- The use of FXIII as a surrogate endpoint for the accelerated approval process.
- Acceptability of supportive PK, safety and preclinical data.
- Acceptability of the post-marketing study to validate the FXIII activity surrogate endpoint.

On August 20, 2007 CBER confirmed that six months of stability data from three commercially produced lots was acceptable for the initial BLA submission with updates during the review period.

On October 31, 2007 CSLB provided the summaries of the 2005 CSLB CQA Audits of Dr. Nugent's study (BB-IND -b(4)-) and CSLB's remediation plan.

On January 08, 2008 CBER suggested to collect new data as the audit summary findings of Dr. Diane Nugent's IND were serious enough to affect the study integrity. It was also suggested to submit the originally proposed FXIII EU PK study synopsis with data for review and acceptability.

On January 25, 2008 CBER cited the risk of using the old IND clinical data generated under violations versus new data. CBER requested data to justify the dosing schedule. CBER referenced the CDC database collection as a possibility for the FXIII clinical program. The originally proposed FXIII EU PK study was discussed and it was suggested by CBER to submit a synopsis of the study with data for evaluation and to determine the acceptability. CBER also suggested the following:

- To continue the corrective action plan with Dr. Diane Nugent to rectify the deficiencies.
- To submit the BB-IND (b)(4) Annual Report to cover the last 7 years.
- To amend the IND protocol to establish a dosing schedule.

On August 15, 2008 CSLB submitted a Factor XIII Type B, Pre-IND meeting request and information package to the FDA. CSLB proposed to support a Biologics License Application (BLA) submission using the accelerated approval program to include:

- A pivotal pharmacokinetic (PK) dosing and safety study.
- Safety data from BB-IND –b(4)– (sponsored by Dr. Diane Nugent)
- Safety data from non-IND European studies, and
- A Phase 3b safety and efficacy post marketing study requirement.

On October 10, 2008 a pre-IND was held: CSLB and OBRR agreed on the following:

- The proposed PK study would serve as the pivotal study, in support of the BLA, and the proposed Phase 3b is designated as the post marketing commitment (PMC) study.
- FXIII levels would be used as the surrogate endpoint in the PK and Phase 2b studies. This surrogate will be used to fulfill the requirements for accelerated approval.
- Source documentation from Dr. Nugent's study would be made available for FDA bioresearch monitoring inspection.
- A dose of 40 U/kg of FXIII at steady state would be used in the PK study.

4.3 Currently Available Treatments for Proposed Indications

Congenital FXIII deficiency is a very rare bleeding disorder that occurs in 1 in 3-5 million individuals. Current treatment and prophylaxis options include cryoprecipitate, fresh frozen plasma (FFP), and preparations of plasma-derived FXIII concentrates.

4.4 Availability of Proposed Active Ingredient in the United States

There is currently no approved FXIII product to treat congenital FXIII deficiency on US market.

4.5 Important Safety Issues with Consideration to Related Drugs

Although cryoprecipitate and fresh frozen plasma provide a source of factor XIII, these products may carry a risk of blood-borne disease, viral transmission, fluid overload, and potential to initiate an immunologic reaction.

5 ETHICS AND GOOD CLINICAL PRACTICES

5.1 Submission Quality and Integrity

The submission has been submitted electronically in accordance to Guidance for Industry: *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format — Biologics Marketing Applications*. The submission is also compliant with ICH guideline M4E, *Common Technical Document for the Registration of Pharmaceuticals for Human Use*, using appropriate numbering within the Modules. An Index provides links to the relevant sections.

5.2 Compliance with Good Clinical Practices

The study protocols and all amendments were approved by the Independent Ethics Committee(s) (IECs) / Institutional Review Board(s) (IRBs) of the participating centers. The studies were carried out in accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice guidelines, the Declaration of Helsinki and standard operating procedures for clinical research and development at CSL Behring (CSLB). An Informed Consent Form (ICF) was prepared by the investigator according to the provisions of International Conference on Harmonisation GCP and was approved by an IEC/IRB prior to use.

5.3 Financial Disclosures

Financial certification and disclosure information (Form 3454) have been submitted. The Applicant certifies that there have been no arrangements where the amount of the compensation could have affected the outcome of the study.

6 TRADE NAME

The trade name CorifactTM has been approved by Advertising and Promotional Labeling Branch (APLB) and OBRR.

7 ORPHAN DRUG STATUS

An Orphan Drug designation was granted to Corifact in January 16, 1985

8 PREA/PeRC

Exempt from PREA because of orphan drug status

9 SOURCES OF CLINICAL DATA

Tables of Studies/Clinical Trials and Sites

The clinical development program for product licensure consist 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. The clinical safety program consists of 12 clinical studies in the following populations:

- 1 study in healthy volunteers,
- 9 studies in congenital Factor XIII deficiency,
- 2 studies in ---b(4)-----.

Brief Synopsis of the study protocols in the following **Table 1**:

Table 1: Efficacy Studies

Study #	Study Design	Population	N	Purpose
2002	Prospective, open-label, single-arm, multi-center	Congenital FXIII Deficiency 5-42y/o	14	PK, efficacy, safety Pivotal, Phase 2
3001	Prospective, open-label, single-arm, multi-center	Congenital FXIII Deficiency 0-42y/o	41 ongoing	Ongoing efficacy, safety, PK, Phase 3b, post-marketing
3002	Prospective, open-label, single-arm, multi-center	Congenital FXIII Deficiency 0-55y/o	24 ongoing	Long-term safety, observational efficacy
5001	Prospective, open-label, single-arm, multi-center	Congenital FXIII Deficiency 0.05-46.9y/o	19	Phase 4, efficacy, safety
5986*	Prospective, open-label, uncontrolled, multi-center	Congenital FXIII Deficiency 0-74y/o	72 ongoing	Phase 2/3, efficacy, safety

* Sponsor's audit summary findings were serious enough to affect the study integrity

Table 1: Safety Studies

Study#	Design	Population	N	Purpose
1003	Prospective, uncontrolled, open-label	Healthy males	20	PK/PD/Safety
7D-101PK	Prospective, randomizes, active- control, crossover	Congenital FXIII Deficiency 24y/o	1	BE/PK/PD/safety (pilot study)
7MN-101PK	Prospective, randomizes, active- control, crossover	Congenital FXIII Deficiency 11-54y/o	13	BE/PK/PD/safety
7MN-101PK (extension)	Prospective, open-label, uncontrolled	Congenital FXIII Deficiency 30-35y/o	2	PK,PD/safety Long-term, follow-up
201	Open-label, uncontrolled	Congenital FXIII Deficiency	4	PK/PD/safety

Study#	Design	Population	N	Purpose
		26-43y/o		
301 CL	Prospective, randomized, placebo-control, 2-arms, multi-center	---b(4)----- ----- 18-47y/o	28	Safety
302 CL	Prospective, randomized, placebo-control, 3-arms, multi-center	---b(4)----- ----- 19-76y/o	33	Safety

Overall Exposure:

In the 12 clinical trials included in this market application, at least 3,930 doses of Factor XIII Concentrate (Human) have been administered. Of these doses of Factor XIII Concentrate (Human), at least 3,590 doses were administered to subjects with FXIII deficiency. This estimated number of infusions includes only an estimation of doses for the long-term 19 subjects study 5001, as this data are not available.

In the Pivotal Study 2002, a total of 41 doses were administered to a total of 14 unique subjects, who received at least one dose of Factor XIII Concentrate (Human).

A total of 173 unique subjects received at least one dose of Factor XIII Concentrate (Human) in the 11 supportive studies. Of these 173 subjects, 35 received Factor XIII Concentrate (Human) in ---b(4)----- Studies 301CL and 302CL. The 2 subjects enrolled in Study 7MN-101PK, extension were also enrolled in Study 7MN-101PK.

(Table 3 extrapolated from the submission):

REVISED Table 3 including 3 month safety Update: Summary of Total Exposure in the Supportive Studies
(BI 71.023/0-1003; BI71023_3001; BI71023_3002; BI 71.023/7D-101PK; BI 71.023/7MN-101PK; BB-IND 5986; B1 71.023/8J/201; CE1232/0-5001; BI 71.023/7MN-101PK, Extension; BI 71.023/7MN-301CL; BI 71.023/7MN-302CL)

Parameter	Healthy Volunteers	Congenital Factor XIII Deficiency								b(4)	
	1003	3001 ^a	3002 ^a	7D-101PK	7MN-101PK	5986	8J/201	5001	7MN-101PK, Extension	301CL	302CL
Development Phase	1	3b	Open Enrollment	1	1	2/3	2	4	1	3	3
Number of Subjects Treated with Factor XIII Concentrate (Human)	20	41	24	1	13	72	4	19	2 ^b	17 ^c	18 ^d
Total administered doses	20	364	80	4 ^e	26 ^f	2745	10	not available ^g	17	166	174

a: As of the cut-off date of 01 October 2010.

b: Subjects were previously enrolled in Study BI 71.023/7MN-101PK.

c: An additional 11 subjects received placebo.

d: An additional 15 subjects received placebo.

e: The subject received two single doses of each of the plasma- and placenta-derived concentrates.

f: All subjects received a single dose of each of the plasma- and placenta-derived concentrates.

g: Treatment was orientated to the recommendations in the French package insert. On entry, the prophylaxis median dose was 9.5 U/kg/week for 12 subjects (range: 2.5 to 16.6 U/kg/week) and the on-demand median dose was 1 U/kg/week for 9 subjects (range: 0.2 to 38.6 U/kg/week). The mean cumulative duration in the study was 677 days (range: 357 to 780 days).

Pivotal Study BI71023-2002 was conducted between May 2009 and February 2010 at the following sites:

Site#/N	Principal Investigator
001 5 subjects	Dr. J. Garcia-Talavera Casanas Canary Islands, Spain
007 1 subject	Dr. Judith C. Lin Boston, Massachusetts
013 2 subjects	Dr. Louise C. Lo San Francisco, California
021 2 subjects	Dr. Aminder S. Mehdi Stockton, California
024 5 subjects	Dr. Claude Ashley Birmingham, Alabama

10 Discussion of Individual Studies/Clinical Trials

10.1. Design: Synopsis

Pivotal Study BI71023_2002 was a multi-center, open-label, single-arm, PK study of Factor XIII Concentrate (Human) in subjects with congenital Factor XIII deficiency. The 40U/kg dose of Factor XIII Concentrate (Human) was administered every 4 weeks for a total of 3 doses over 12 weeks. The study planned to enroll 15 subjects to allow for at least 12 evaluable subjects, the number required for a satisfactory evaluation of steady-state PK data. The study duration was 16 weeks; a 4-week screening period and a 12-week treatment period.

10.2 Objective(s)

Primary Objective

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

Secondary Objective

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

10.3 End points

Factor XIII level was evaluated as the surrogate endpoint. The effectiveness of a dosing regimen of 40 U/kg of Factor XIII Concentrate (Human) every 28 days was assessed by achieving a Factor XIII level $\geq 5\%$. The effectiveness of Corifact was evaluated based on a surrogate marker of maintaining a trough FXIII activity level of approximately $\geq 5\%$ to 20%. Based on historic evidence, maintaining a trough Factor XIII level of $\geq 5\%$ was selected as the surrogate endpoint for hemostatic efficacy for Factor XIII replacement therapy. Maintaining the trough FXIII activity level at Day 28 between 5% -20% is expected to prevent breakthrough bleeding in congenital FXIII deficient patients, and was therefore used as a surrogate marker in the pivotal study BI71023_2002. A post-marketing study to validate the surrogate endpoint by showing a correlation between trough levels of FXIII (5% to 20%) and clinical efficacy is currently ongoing.

10.4 Inclusion/Exclusion Criteria

Inclusion Criteria:

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

Exclusion Criteria:

- Diagnosis of acquired Factor XIII deficiency,
- Administration of a Factor XIII-containing product, including blood transfusions or other blood products within 4 weeks prior to the planned Day 0,
- Any known congenital or acquired coagulation disorder other than congenital Factor XIII deficiency,
- Known or suspected to have antibodies towards Factor XIII,
- Use of any other IMP within 4 weeks prior to the baseline visit (Day 0),
- Positive result at screening for HIV,
- Serum aspartate transaminase (AST) or serum alanine transaminase (ALT) concentration >2.5 times the upper limit of normal,
- Fibrinogen $<$ lower limit of normal,
- Active bleeding,
- Pregnant or breast feeding,
- Intention to become pregnant during the course of the study,
- 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,
- Surgical procedure anticipated during the study period, and
- Suspected inability (e.g., language problems) or unwillingness to comply with study procedures or history of noncompliance.

10.5 SAP

Pivotal Study BI71023-2002 is a PK and safety study. Therefore no formal testing of hypotheses was performed. Descriptive statistics (n, mean, SD, median, minimum, and maximum, along with geometric mean, geometric percent coefficient of variation [%CV], and 95% CIs around the geometric mean) were used to summarize Factor XIII levels for the overall study population and by gender, age, and race. Linear and semi-logarithmic plots of the mean and individual Factor XIII levels were generated separately for each subject and for the overall study population. Pharmacokinetic parameters were assessed individually for Factor XIII activity using a non-compartmental model. Standard formulae (e.g., -----(b)(4)-----) were used to calculate individual PK variables without and with adjustment for any unknown remaining endogenous Factor XIII levels. The steady-state PK parameters were calculated using non-compartmental methods as data permit following Dose 3. (*Full statistical details are to be found at Dr. Renee Rees' Statistical Review.*)

As agreed upon during the pre-BLA meeting (March 10, 2010), the Applicant 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*.

Analysis populations

The reasons for exclusion of subjects from either the safety or primary analysis (PK) populations were documented.

Safety population:

The safety population consisted of all subjects who received a dose of Factor XIII during the study (N=14). All safety analyses were performed on the safety population.

Primary analysis (pharmacokinetic) population:

The PK population consisted of all subjects in the safety population who completed the study (defined as having sufficient bioanalytical assessments to calculate reliable estimates of the PK parameters specified). Up to 15 subjects were to be treated in order to obtain at least 12 subjects in the primary analysis (PK) population. The primary analysis (PK) population (N=13) was used to assess the PK of Factor XIII.

**Primary analysis population and PK population terms are used interchangeably.*

10.6. Post-Marketing Phase 4 Study

Synopsis:

Post-marketing Phase 4 study (Study No BI71023_3001) is ongoing and will include 41 subjects. It is a multi-center, prospective, open-label study. [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 cut-off).] 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. Approximately 40 subjects will be enrolled to obtain 32 evaluable (per protocol) subjects. Efficacy endpoints are the frequency and severity of bleeding episodes following prophylactic treatment. The primary endpoint is the annual incidence of spontaneous bleeding events requiring administration of a Factor XIII-containing product to treat the bleeding event.

Primary objective: collect and evaluate the 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.

Study Design and Endpoints

This multi-center, prospective, open-label, Phase 3b study is ongoing. The 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 annual incidence 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).

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 Applicant 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. The sample size calculation is based on the assumption of the study to detect (with a one-sided level of significance less than 0.025 and power greater than 90%) a reduction of at least 50% in the incidence of spontaneous bleeding events under prophylactic treatment as compared to the incidence density of 2.5 events per person per year that was observed in the historical control group.

All summary tables provided by the Applicant 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.

11 REVIEW OF EFFICACY

Efficacy summary

Pivotal Study BI71023-2002 was primarily a PK and safety study. Therefore no formal testing of hypotheses was performed. All PK parameters were assessed using both standard and amended Berichrom assay. The amended potency assay is calibrated against the current 1st *International Standard for Blood Coagulation Factor XIII, Plasma*. The standard potency assay was calibrated against a commercially available FXIII plasma standard (----(b)(4)-----). FXIII activity of this plasma standard is determined by the manufacturer by comparison to the FXIII activity in a pool of fresh plasma samples from

healthy donors. A comparison of the standard versus the amended potency assay showed the result to be equivalent. The PK results are summarized elsewhere in this document. Five (35.7%) subjects in the study population were <16 year old. Subjects less than 16 years had a shorter half life (5.7 ± 1.00 days) and faster clearance (0.29 ± 0.12 mL/hr/kg) compared to adults (half life: 7.1 ± 2.74 days, clearance: 0.22 ± 0.07 mL/hr/kg). The number of subjects less than 16 years of age limits the statistical interpretation, however there were no apparent differences in the safety profile in children as compared to adults.

11.1 Indication

The surrogate efficacy endpoint, trough FXIII level of $\geq 5\%$ is expected to predict the clinically meaningful effect of Factor XIII replacement therapy.

11.1.1 Methods

Descriptive statistics (n, mean, SD, median, minimum, and maximum, along with geometric mean, geometric percent coefficient of variation [%CV], and 95% CIs around the geometric mean) were used to summarize Factor XIII levels for the overall study population and by gender, age, and race. Linear and semi-logarithmic plots of the mean and individual Factor XIII levels were generated separately for each subject and for the overall study population. Pharmacokinetic parameters were assessed individually for Factor XIII activity using a non-compartmental model.

11.1.2 Demographics

The demographic characteristics are described for the safety population of Pivotal Study BI71023-2002 [these are subjects who received at least one dose of Factor XIII Concentrate (Human)], half were female (50.0%), approximately one-third (35.7%) of the subjects were Caucasian and one-third (35.7%) Black/African American; 2 subjects (14.3%) were Asian and 2 subject (14.3%) were Hispanic. 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. All of subjects had a documented congenital Factor XIII deficiency. The demographic data are summarized in **Table 4** (*extrapolated from the submission*):

**Table 4: Demographic Characteristics in the Pivotal Study
(BI71023_2002, Safety Population)**

	(N=14)
Age at Screening (years)	
Mean (SD)	24.0 (12.55)
Median (range)	26.5 (5 – 42)
Age group at Screening, n (%)	
<16 years	5 (35.7)
16-<65 years	9 (64.3)
≥65 years	0
Gender, n (%)	
Male	7 (50.0)
Female	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)	158.3 (18.40)
Median (range)	162.6 (108 – 177)
Weight (kg)	
Mean (SD)	67.69 (21.835)
Median (range)	73.10 (18.5 – 102.1)
Age at Diagnosis (years)	
Mean (SD)	6.3 (7.91)
Median (range)	4.5 (0 – 26)
Age group at Diagnosis, n (%)	
<16 years	12 (85.7)
16-<65 years	2 (14.3)
≥65 years	0

Source: [Module 5.3.3.2](#); [Table 14.1.2.1](#).

11.1.3 Subject Disposition

Thirteen of the 15 enrolled subjects (86.7%) in pivotal Study BI71023-2002 completed the study; 1 subject (6.7%) was discontinued from the study due to withdrawal of consent. An additional subject met the eligibility criteria but was not enrolled as per the Applicant's administrative decision. After screening and prior to treatment of this subject, the number of evaluable subjects needed for the study had been met and enrollment was closed in order to meet program timelines.

11.1.4 Sites (US/out of US)

The pivotal study was conducted at five sites. Study Site 001 Canary Islands, Spain (5 subjects); Study Site 007 Boston, Ma, USA (1 subject); Study Site 0013 San Francisco, California, USA (2 subjects); Study Site 021 Stockton, CA, USA (2 subjects); Study Site 024 Birmingham, AL, USA (5 subjects)

Site#/N	Principal Investigator
001 5 subjects	Dr. J. Garcia-Talavera Casanas Canary Islands, Spain
007 1 subject	Dr. Judith C. Lin Boston, Massachusetts
013 2 subjects	Dr. Louise C. Lo San Francisco, California
021 2 subjects	Dr. Aminder S. Mehdi Stockton, California
024 5 subjects	Dr. Claude Ashley Birmingham, Alabama

11.1.5 Randomization

Randomization is not applicable.

11.1.6 Protocol Violations

-----redacted per Privacy Act-----

 -----redacted per Privacy Act-----

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11.1.7 Analysis of Primary Endpoint(s)

There was no primary efficacy variable in the 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. (The post-marketing requirement safety and efficacy Phase 4 Study is to prove the relation of the surrogate endpoint to clinical benefit (hemostasis). 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.

The PK study showed that in patients with FXIII deficiency the study product 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. (*For the full details on PK studies, please refer to Dr. Iftekhar Mahmood's review.*)

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
$AUC_{(0-\infty)}$	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
V_{ss}	58 ± 15	53 ± 12	67 ± 20	51 ± 13	50 ± 13	61 ± 19

Units of $AUC_{(0-\infty)}$ = 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 = hrs

*The amended potency assay is calibrated against the current 1st International Standard for Blood Coagulation Factor XIII, Plasma. The standard potency assay was calibrated against a commercially available FXIII plasma standard (----(b)(4)-----). FXIII activity of this plasma standard is determined by the manufacturer by comparison to the FXIII activity in a pool of fresh plasma samples from healthy donors. A comparison of the standard versus the amended potency assay shows the result to be equivalent.

Pediatric subjects:

Five (35.7%) subjects in the study population were <16 year old. Subjects less than 16 years had a shorter half life (5.7 ± 1.00 days) and faster clearance (0.29 ± 0.12 mL/hr/kg) compared to adults (half life: 7.1 ± 2.74 days, clearance: 0.22 ± 0.07 mL/hr/kg). The number of subjects less than 16 years of age limits the statistical interpretation.

11.1.8 Secondary Endpoints

Safety and tolerability of Factor XIII (Human)

Efficacy Analysis of the ongoing Phase4 study on the available data:

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.

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.

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

The projected end of the study is April 17, 2011 (the date of the last follow-up visit), the Final Study Report is to be submitted to the FDA by December 31 2011.

12 REVIEW OF SAFETY

Safety Summary

The safety program consists of 12 clinical studies. In these 12 studies, a total of 187 unique subjects received at least one dose of FXIII Concentrate (Human). An estimated total of 3930 doses of FXIII Concentrate (Human) were administered, 3590 of which were administered to subjects with congenital FXIII deficiency (35 of the study subjects did not have congenital FXIII deficiency).

The safety of Factor XIII administration was evaluated via adverse events (AEs), laboratory assessments, vital signs, and physical examination results. Development of FXIII inhibitors was tested in 9 studies. The summaries were performed using the safety population. Safety population is defined as subjects who received at least one dose of Corifact.

There were no deaths, life-threatening events or adverse events that led to study discontinuation in the pivotal study to support this BLA application. Eight subjects in the study experienced treatment-emergent adverse events (TEAE) of mild to moderate severity (5 subjects experienced infections, injury, bruising and contusion, ecchymosis, borderline diabetes), three subjects within 24 hours, three subjects within 72 hours of infusion. No episodes of thrombo-embolism or viral transmission were identified during the study. The two occurrences of laboratory increases (thrombin-antithrombin III complex increased and prothrombin increased and fibrin D-dimer increased) were not associated with any clinical signs of thrombo-embolism, and were possibly related. One subject experienced a mild rash on Day 65 that was considered unrelated to study product and was ongoing.

There was one case of thrombogenicity and one case of immunogenicity described in the clinical development for FibrogaminP (trade name of Corifact in EU):

BLA safety data cut-off date was February 15, 2010. In the 3-month Safety Update FDA received in November 2010, the Applicant reports a Serious Adverse Event in the Study 3002, which is part of the post-marketing Phase 4 clinical program. The 26-year old subject with congenital FXIII deficiency was hospitalized and treated for clinical symptoms consistent with a neutralizing inhibitor to Factor XIII, which was deemed a study treatment related SAE.

A serious AE of Myocardial Infarction was reported in an -----b(4)----- study (Study 302 CL. Eleven subjects experienced an AE of hypersensitivity symptoms.

There was no proven case of virus transmission by Factor XIII concentrate in the clinical development of Corifact.

12.1 Methods

12.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pivotal Study BI71023-2002 for the market application was conducted March 2009 through February 2010. It was an uncontrolled, single-arm PK study in subjects with congenital FXIII deficiency.

Included in the submission are supportive safety data from the following non-IND studies.

- **Study BI71.023/0-1003**, hereafter referred to as Study 1003: An open-label, single-arm, uncontrolled Phase 1, single dose PK study in 20 healthy volunteers conducted between April 1997 and October 1997.

Safety Conclusions: A total of 6 AEs in 4 subjects were considered mild and possibly related to the administered study drug (bilirubinemia, Gamma-GT increased, SGOT increased and SGPT increased, sinus bradycardia and EEG abnormal).

- **Studies BI71023_3001 and BI71023_3002**, hereafter referred to as Study 3001 and 3002: and open-label, single-arm, multi-center Studies 3001 and 3002. Both studies are ongoing:

Study3001:

Twenty-seven (27) subjects were enrolled as of the BLA safety cut-off date of 15 February 2010, with 16 of those subjects being unique. An interim safety report was submitted as part of the BLA application. Twenty seven subjects, who were also included in the safety population, received at least one dose of Factor XIII Concentrate (Human) in total of 81 infusions, amounting to 7042.93 Units.

Safety Conclusions: One subject was diagnosed with atypical chest pain on Day 98. His EKG revealed sinus bradycardia. Cardiac enzymes and troponin were repeatedly negative. The subject was followed up by gastroenterologist. One subject experienced TEAE of thrombin-antithrombin elevation, with no association to a thrombotic event. The study is ongoing.

Study 3002:

This ongoing multi-center, prospective, open-label, uncontrolled Phase 3b study was initiated on September 2009 and is ongoing. It was designed to allow administration of Factor XIII Concentrate (Human) to United States subjects with congenital Factor XIII deficiency until CSLB's Factor XIII Concentrate (Human) becomes commercially available.

Three (3) subjects were enrolled as of the BLA cut-off date of 15 February 2010 with all 3 subjects being unique. A total of 24 subjects (13 unique) have received Factor XIII Concentrate (Human) and have been entered into the clinical Study 3002 database.

Safety Conclusions: One subject (out of three) reported common cold. In the 3-month Safety Update FDA received in November 2010, the Applicant reports a Serious Adverse

Event of inhibitor development in the Study 3002. (*see 13 POST-MARKETING EXPERIENCE*)

•**Study BI71.023/7D-101PK**, hereafter referred to as Study 7D-101PK: A randomized, double-blind, active-controlled, two-way crossover, pilot Phase 1 study, 2 doses of 30U/kg PK study, one subject conducted between August 1991 and June 1992.

Safety Conclusions: The patient suffered a mild AE unrelated to study drug; epistaxis

•**Study BI71.023/7MN-101PK**, hereafter referred to as Study 7MN-101PK: A randomized, double-blind, active-controlled, two-way crossover Phase 1 single-dose PK study in 13 subjects. Control: Factor XIII Concentrate (Human) --b(4)----- Single dose of 30 U/kg, conducted between January 1992 and April 1993.

Safety Conclusions: Two patients developed small hematomas (mild AE), there were few mild AEs (cold, facial rash, throat pressure, erythema, slight temperature elevation, finger sprain), one moderate AE (headache).

•**Study BI71.023/8J/201**, hereafter referred to as Study 8J/201: An open-label, single-arm, uncontrolled Phase 1 single-dose with follow-up doses PK study in 4 subjects conducted between October 1992 and March 1993.

Safety Conclusions: No adverse events reported.

•**Study BI71.023/7MN-101PK**, hereafter referred to as Study 7MN-101PK [extension]: An open-label, single-arm, uncontrolled Phase 1 efficacy and safety in 2 subjects, one received 8 single doses, one 9, long-term, follow-up, conducted between January 1993 and October 1993.

Safety Conclusions: Two mild AEs unrelated to study drug were; suspicion of tubal infection and paresthesia.

•**Study CE1232/0-5001**, hereafter referred to as Study 5001: An open-label, single-arm, uncontrolled Phase 1 safety study in 19 subjects, prophylactic median dose, than on-demand conducted between March 1999 and July 2001.

Safety Conclusions: Two AEs were reported. One patient developed migraine of moderate intensity, one patient an allergic reaction of mild intensity.

•**BB-IND- -b(4)-**, Study 5986: An open-label, uncontrolled, US investigator-initiated PK study in 72 subjects provides additional safety data. This study was initiated in January 2000 and is ongoing. The cut-off date for inclusion in this market application is 31 December 2008. Any additional serious adverse events (SAEs) that occurred after this date and before 31 March 2010 are included in this application.

Safety Conclusions: Three subjects had SAEs that resulted in death (gun shot, road traffic accident and hypertension). None of the events were related to treatment with FXIII. No thrombo-embolic events were reported during the study. One subject experienced an AE of hypersensitivity. The event was rated by the investigator as moderate in severity and related to treatment with Factor XIII Concentrate (Human). Eight subjects reported AEs that may have been associated with hypersensitivity reaction. A reactivation of pre-existing hepatitis C infection and a seroconversion of parvovirus B19 antibody were

[illegible]

12.1.2 Categorization and Summary of Adverse Events

There were no Deaths and/or Serious Adverse Events (SAEs) reported in the pivotal study. There were no study discontinuations due to AEs as well. Eight subjects (57.1%) reported at least one treatment-emergent AE during the study. Two subjects (14.3%) reported possibly related AEs. All AEs were mild or moderate in severity. The most frequently reported treatment-emergent AE was acute bronchitis (14.3%). All remaining treatment-emergent AEs were reported by 1 subject (7.1%) each. The Treatment – Emergent Adverse Events (TEAEs) are summarized in the Table 6 (*extrapolated from the submission*):

Type of AE	2002 (N=14)
At least 1 treatment-emergent AE	8 (57.1)
At least 1 possibly related treatment-emergent AE	2 (14.3)
At least 1 treatment-emergent SAE	0
At least 1 possibly related treatment-emergent SAE	0
At least 1 treatment-emergent AE leading to permanent treatment discontinuation	0
Death	0

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12.2 Major Safety Results

12.2.1 Deaths

There were no deaths in the pivotal study.

12.2.2 Nonfatal Serious Adverse Events

There were no Serious Adverse Events in the pivotal study.

12.2.3 Dropouts and/or Discontinuations

1 subject (6.7%) was discontinued from the study due to withdrawal of consent. An additional subject met the eligibility criteria but was not enrolled because of the Applicant's administrative decision.

12.2.4 Significant Adverse Events

There were no deaths, life-threatening events or adverse events that led to study discontinuation in the pivotal study to support this BLA application. Eight subjects in study experienced treatment-emergent adverse events (TEAE) of mild to moderate severity (5 subjects experienced infections, injury, bruising and contusion, ecchymosis, borderline diabetes), three subjects within 24 hours, three subjects within 72 hours of infusion. No episodes of thrombo-embolism or viral transmission were identified during the study. The two occurrences of laboratory increases (thrombin-antithrombin III complex increased and prothrombin increased and fibrin D-dimer increased) were not associated with any clinical signs of thrombo-embolism, and were possibly related. One subject experienced a mild rash on Day 65 that was considered unrelated to study product and was ongoing.

12.3 Supportive Safety Results

Summary of Treatment –Emergent Adverse Events in the supportive studies

Table 7: Summary of Treatment-Emergent Adverse Events in the Supportive Studies
(BI 71.023/0-1003; BI71023_3001; BI71023_3002; BI 71.023/7D-101PK; BI 71.023/7MN-101PK; BB-IND 5986; BI 71.023/8J/201; CE1232/0-5001; BI 71.023/7MN-101PK, Extension; BI 71.023/7MN-301CL; BI 71.023/7MN-302CL)

Type of AE	Study n (%)										
	Healthy Volunteers	Congenital Factor XIII Deficiency								Ulcerative Colitis	
	1003 (N=20)	3001 ^a (N=41)	3002 ^a (N=24)	7D-101PK (N=1)	7MN-101PK (N=13)	5986 (N=72)	8J/201 (N=4) ^b	5001 (N=19)	7MN-101PK, Extension (N=2)	301CL (N=28)	302CL (N=33)
At least 1 treatment-emergent AE	8 (40.0)	12 (29.3)	12 (50.0)	1 (100.0)	6 (46.2)	40 (55.6)	0	2 (10.5)	2 (100.0)	3 (10.7)	8 (24.2)
At least 1 possibly related treatment-emergent AE	4 (20.0)	1 (2.4)	1 (4.2)	0	4 (30.8)	3 (4.2) ^c	0	1 (5.3)	0	2 (7.1)	2 (6.1)
At least 1 treatment-emergent SAE	0	1 (2.4)	1 (4.2)	0	0	8 (11.1) ^d	0	1 (5.3)	0	0	1 (3.0)
At least 1 possibly related treatment-emergent SAE	0	0	1 (4.2)	0	0	0	0	0	0	0	1 (3.0)
At least 1 treatment-emergent AE leading to permanent treatment discontinuation	0	0	0	0	0	3 (4.2)	0	0	0	0	0
Death	0	0	0	0	0	3 (4.2)	0	0	0	0	0

a: As of the cut-off date of 01 October 2010.

b: Safety was assessed using the following 4 stages, in consideration of whether accompanying symptoms occurred after dosing with the drug, and whether there were any abnormal changes in the clinical laboratory test values: safe, mostly safe, questionable safety, and not safe. None of the subjects showed any significant changes in vital signs.

c: The relationship to study drug was missing for 4 subjects.

d: The categorization of AEs as serious or not was missing for 3 subjects. Two additional subjects reported SAEs following the cut-off date (31 December 2008) (see [Section 2.7.4.2.1.3](#)).

Most common ($\geq 1\%$) treatment-emergent AEs in all 187 unique subjects exposed to Factor XIII Concentrate (human) **Table 8** (*extrapolated from the submission*):

Table 8: Summary of Common ($\geq 1.0\%$ [>1 Subject]) Treatment-Emergent Adverse Events in the Factor XIII Concentrate (Human) Clinical Program

System Organ Class Preferred Term	(N=187) n (%)
Body as a Whole	
Flu syndrome	4 (2.1)
Gastrointestinal Disorders	
Abdominal pain	4 (2.1)
Diarrhea 4	(2.1)
Vomiting 4	(2.1)
Nausea 3	(1.6)
Abdominal pain upper	2 (1.1)
General Disorders and Administration Site Conditions	
Pyrexia 4	(2.1)
Fatigue 3	(1.6)
Pain 3	(1.6)
Chest pain	2 (1.1)
Edema peripheral	2 (1.1)
Immune System Disorders	
Seasonal allergy	2 (1.1)
Injury, Poisoning and Procedural Complications	
Contusion 17	(9.1)
Joint injury	7 (3.7)
Limb injury	4 (2.1)
Road traffic accident 4	(2.1)
Head injury	4 (2.1)
Bruising 3	(1.6)
Joint sprain	3 (1.6)
Face injury	2 (1.1)
Medical device complication	2 (1.1)
Infections and Infestations	
Upper respiratory tract infection	4 (2.1)
Otitis media	3 (1.6)
Acute bronchitis	2 (1.1)
Ear infection	2 (1.1)
Infection 2	(1.1)
Sinusitis 2	(1.1)
Urinary tract infection	2 (1.1)
Investigations	
Blood lactate dehydrogenase increased	2 (1.1)
Thrombin-antithrombin III complex increased ^a	2 (1.1)
Musculoskeletal and Connective Tissue Disorders	
Arthralgia 6	(3.2)
Musculoskeletal pain	3 (1.6)
Pain in extremity	3 (1.6)
Back pain	2 (1.1)
Nervous System Disorders	
Headache 6	(3.2)
Migraine 3	(1.6)
Convulsion 2	(1.1)
Loss of consciousness	2 (1.1)
Respiratory, Thoracic and Mediastinal Disorders	
Epistaxis 4	(2.1)

Table 8: Summary of Common ($\geq 1.0\%$ [>1 Subject]) Treatment-Emergent Adverse Events in the Factor XIII Concentrate (Human) Clinical Program (Continued)

System Organ Class Preferred Term	(N=187) n (%)
Skin and Subcutaneous Tissue Disorders	
Rash 7	(3.7)
Ecchymosis 3	(1.6)
Surgical and Medical Procedures	
Dental care	2 (1.1)
Tooth extraction	2 (1.1)
Vascular Disorders	
Hematoma 4	(2.1)

Note: As of the cut-off date of 01 October 2010.

b(6)

For labeling purposes, AEs were listed based on the investigator relationship assessment, the assumption of relatedness if relationship is missing, and grouping related AEs under similar disease process terms. The following terms were reported and considered associated with the use of Factor XIII Concentrate (Human) at a rate of $>1\%$ (>1 subject): hypersensitivity (including allergy, rash, pruritis, erythema, hypersensitivity), chills/rise in temperature, arthralgia, thrombin-antithrombin III complex increased, headache, and an increase in hepatic enzymes (including SGOT increased, SGPT increased, Gamma GT increased, and hepatic enzyme increase).

13 POST-MARKETING EXPERIENCE

Between June 1993, when licensure of pasteurized/heat-treated plasma-derived product took place, and 30 September 2010, a total of 52 spontaneous reports of suspected ADRs, were collected from the worldwide market, including two cases received from investigator sponsored (non-interventional) studies. The post-marketing surveillance system captured data via spontaneous reports, reports from the scientific literature, and reports from investigator sponsored studies of suspected adverse drug reactions (ADRs). The number of ADR reports was compared to the number of estimated single standard doses. The estimated single standard dose for Factor XIII Concentrate was 750 IU. During this period, -----(b)(4)----- IU of Factor XIII concentrate were distributed, corresponding to ---(b)(4)--- estimated single standard doses (750 IU). This reflected an overall reporting rate of 1 report---(b)(4)----- estimated single standard doses.

Of the 52 spontaneous reports of suspected ADRs, approximately 63% (33/52) were considered expected. Nineteen reports were classified as unexpected. Those reports do not represent any clusters but are single cases of different symptoms that did not effect the above safety profile.

Thrombo-Embolic Complications:

Three case reports contained AE terms of thrombo-embolic complications. All three cases were assessed as serious, one as unlikely and two as possibly related to the FXIII concentrate administration.

Case 1 and Case 2 were thrombo-embolic events in patients with no known FXIII deficiency. Fibrogamin P was administered for the suture insufficiency in both cases. These two cases were reported from Japan, where Factor XIII Concentrate (Human) is approved as supportive therapy for disturbance in wound healing after large surgeries.

1. Case ----(b)(6)----- concerns a 51-year-old female patient who was treated with Factor XIII concentrate for suture insufficiency after head of caput pancreatic-duodenotomy from 01 January 1999 to 03 January 1999. In the context of postoperative fulminant hepatitis with suspected marked postoperative liver damage, the patient developed DIC. The causality to Factor XIII concentrate administration was assessed as unlikely.
2. Case ----(b)(6)----- concerns a 7-day-old male with asplenia syndrome, univentricular heart and single atrium, total anomalous pulmonary venous connection, and pulmonary congestion with postoperative chylothorax who was treated with Factor XIII concentrate and fresh frozen plasma. The patient developed embolism, suspicion of cerebral embolism, suspicion of shunt occlusion, and sudden cardiac arrest after removal of a CV catheter after cardiac surgery under extracorporeal circulation. The case outcome was fatal. The causality to Factor XIII concentrate administration for this case was assessed as possible. However, cardiac surgery and CV lines are additional causative agents for thrombus formation.
3. Case ----(b)(6)--- concerns a 69-year-old male diagnosed with congenital severe Factor XIII deficiency in 1990. In September 2006, the patient presented to a local hospital with chest pain. He had administered 750 U (9 U/kg) of Factor XIII concentrate 7 days prior to presentation, during which time he also had experienced symptoms of unstable angina. Electrocardiogram revealed mild anterior ST elevation and inferior ST depression consistent with anterior MI. He received a loading dose of clopidogrel (600 mg) combined with enoxaparin (0.85 mg/kg s.c.) and tirofiban IV, in association with Factor XIII replacement of 1250 U (15 U/kg). Aspirin, fibrinolytics, and IV low molecular weight heparin were initially avoided because of his bleeding disorder characterized with impaired fibrin-stabilizing activity. Coronary angiography 8 hours later revealed a total occlusion of the left anterior descending artery. PTCA with a metal stent was successfully performed without subsequent bleeding or thrombotic complications. The patient

recovered completely and was discharged 7 days after admission. The causality to Factor XIII Concentrate administration was assessed as possible, although the patient had multiple other risk factors.

Deaths:

Five fatal case reports were received. One case of fatal septic shock after surgical evacuation of hemoperitoneum, one case of fatal hepatic coma, one case of intracranial hemorrhage in a premature baby, and one case of fatal interstitial pneumonia. For these four cases, the causality to Factor XIII concentrate administration was assessed as unlikely. The fifth case concerned a 7-day-old male with asplenia syndrome, univentricular heart and single atrium, total anomalous pulmonary venous connection, and pulmonary congestion who developed embolism and sudden cardiac arrest after removal of a central venous catheter after cardiac surgery under extracorporeal circulation. The causality to Factor XIII concentrate administration for this case was assessed as possible because the fibrin-stabilizing effect of Factor XIII concentrate may have contributed to the formation of thrombosis and embolism. However, cardiac surgery and central venous lines are additional causative agents for thrombus formation.

Inhibition of Factor XIII:

Three patients are reported in the scientific literature to develop inhibitors against Factor XIII. In clinical trials conducted with Fibrogammin P, no development of inhibitors was found until after the BLA data cut-off date.

In the 3-month Safety Update FDA received in November 2010, the Applicant reports a Serious Adverse Event of inhibitor development in the Study 3002, which is a part of the post-marketing clinical program:

The subject (b)(6) was hospitalized and treated for clinical symptoms consistent with a transient neutralizing inhibitor to Factor XIII. The subject was a 26-year-old Caucasian female diagnosed with congenital Factor XIII deficiency as an infant that entered the Phase 3b Study 3002 on 19 April 2010. The subject had been treated with Factor XIII Concentrate (Human) in investigator-initiated Study 5986 since December 2000. Her first dose in Study 3002 was on 20 April 2010 at 40 U/kg (2628 U) every 4 weeks. She was started on interferon and ribavirin for her active hepatitis C in October 2009.

This treatment regimen was tolerated until 22 July 2010 when she complained of increased bruising. On 30 July 2010, the decision was made to treat the subject every 2 weeks rather than monthly (03 August 2010 [60 U/kg] and 17 August 2010 [50 U/kg]). On 17 August 2010, immediately after the Factor XIII Concentrate (Human) infusion, the subject began complaining of a cutaneous hypersensitivity reaction that was successfully treated with 50 mg of oral diphenhydramine. She was placed on a daily dose of oral steroids on 17 August 2010 (prednisone 20 mg daily on 17 August 2010 for 4 days; 20 mg twice a day started on 20 August 2010; switched to 30 mg once a day).

It was noted that her peak activity and antigen levels following administration of Factor XIII Concentrate (Human) were continuing to decline and bleeding symptoms

(increase in bruising and large hematomas) were reoccurring at closer intervals from the time of dosing. As a result, the Factor XIII Concentrate (Human) dose was changed to 50 U/kg and the infusion frequency was increased from every 2 weeks to weekly. The subject received 100 U/kg on 23 August 2010, after being pre-medicated to avoid a hypersensitivity reaction. On 29 August 2010, the subject presented with complaints of increased bruising. Bruising was primarily in the left leg/thigh, left groin hematoma, and right lateral ankle. Hematomas were confirmed by magnetic resonance imaging. On 30 August 2010, the subject was again pre-medicated and given 200 U/kg (11,400 units) of Factor XIII Concentrate (Human), but developed a hypersensitivity reaction with wheezing, shortness of breath, chest tightness, and urticaria.

Due to concerns that the interferon regimen may be contributing to her decreased Factor XIII recovery and other immune reactions, the interferon regimen was discontinued on 19 August 2010. Her problems with substance abuse were documented during this hospitalization; she was arrested for this reason as an inpatient. For subject safety and expediency, on 31 August 2010, the -----
----- (b)(4) ----- to detect Factor XIII antibodies. The assay does not measure the neutralizing activity of the antibody and was not validated for this study.

The results of this test were positive for Factor XIII subunit A, immunoglobulin G (IgG) subtype antibodies. All samples, including at study baseline (20 April), were positive for antibodies against Factor XIII. Baseline values from 20 April 2010 were weakly positive and became increasingly positive. Validated tests were not performed by the designated laboratory at that time due to internal assay issues. Results using the validated ----- (b)(4) ----- demonstrated evidence of weak inhibitor formation on the plasma sample drawn on 03 August 2010 (see table below; results were reported in October 2010). Samples drawn on 14 September 2010 again became negative for inhibitors.

Between 02 September 2010 and 14 September 2010, the subject received 8 rounds of plasmapheresis. The subject has had an internal jugular catheter in place for nearly 2 weeks and it was clinically presumed to be infected. The line was removed on 15 September 2010; a new internal jugular catheter was inserted after the subject's infusion of 200 U/kg on 17 September 2010. During the last round of plasmapheresis on 14 September 2010, the subject was pre-medicated prior to being treated with Factor XIII Concentrate (Human) at 100 U/kg. The subject had a very mild reaction (itching) and received an additional 25 mg diphenhydramine after the infusion.

The subject was discharged from the hospital on 20 September 2010 with plans for close follow-up. At the 24 September 2010 visit, there were no complaints of increase bruising or bleeding. Laboratories received post-hospital discharge revealed that as of 07 September 2010, her Factor XIII recovery had improved.

Viral Transmission:

Within the reporting period, there was no proven case of virus transmission by Factor XIII concentrate.

14 ADVISORY COMMITTEE MEETING

This BLA application was not referred to the Blood Products Advisory Committee because the manufacture of Factor XIII Concentrate (Human) employs a process using conventional adsorption, precipitation and chromatographic methodologies that are common in the manufacture of other plasma-derived products. It has been on the market outside the U.S. since 1993. The mechanisms of action of Factor XIII Concentrate (Human) and its role in blood coagulation are well understood. Our review of information submitted in the BLA, including the clinical study design and trial results, did not raise concerns or controversial issues. FXIII (Human) is a well known biologic entity, therefore no novel concerns were raised in this application that would require and/or benefit from an advisory committee.