

Pharmacology/Toxicology Review - Filing of Final Non-Clinical Review- Corifact

To: File (STN 125385 Original BLA)

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Subject: Filing of Final Non-Clinical Review of STN 125385/0 - CSL Behring's Original Biological License Application for Human Factor XIII Concentrate, Pasteurized Corifact™

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I. Executive Summary

Corifact™ was determined to be safe as a FXIII replacement therapy based on its pre-clinical program (GLP and non-GLP studies); and its long-standing clinical history and experience being marketed in Europe since 2004. The non-clinical program for Corifact™ consisted of a battery of studies to demonstrate the safety and effectiveness of the product. Pre-clinical studies were conducted for local tolerance (rabbit), acute dose toxicity (rat and mice), repeat dose toxicity (rat), safety pharmacology and efficacy (rat, FXII knock-out mice, and Hemophilia A dogs), and pharmacokinetics (rat) at doses ranging from clinical dose up to ten fold maximal clinical dose. The safety profile demonstrated for Corifact™ is sufficient to support biological license application approval. Animal models for FXIII deficiency and wound treatment demonstrate a reduction in blood loss and improved time to hemostasis and clot strength following Corifact™ administration. *In vitro* and *in vivo* mutagenesis and carcinogenesis studies or studies to address the potential of long-term effects from product have not been

performed with Corifact™. Antigenicity (rabbit and guinea pig) and thrombogenicity studies (rabbit) were performed using Corifact™ and the results indicate that Corifact™ is likely not antigenic; and does not cause thrombogenicity up to fifteen times acute clinical dose. Taken together, Corifact™ appears safe enough for its intended indication based on these data. Previous experience with Factor XIII replacement therapy indicates a potential for anaphylactic reactions, inhibitor development, thromboembolic events, and rarely, transmission of disease when administered. Post-marketing clinical studies will address concerns for immunogenicity related to Corifact™ clinical use.

Recommendation:

The Pharmacology/Toxicology Reviewer recommends Biological License Application approval for Corifact™ .

II. Non-clinical Labeling for Final Package Insert (PI)

The following is the final Pharmacology/Toxicology label:

13.2 Animal Toxicology and/or Pharmacology

Corifact was studied in an acute toxicity study in mice and rats at doses up to 3550 U per kg and 1420 U per kg, respectively. Repeat dose toxicity was studied in rats at daily doses up to 350 U per kg for a period of 14 days. No signs of toxicity were observed in the single dose and repeat dose studies.

A local tolerance study demonstrated no clinical or pathohistological changes at the injection site after intravenous, intraarterial or paravenous administration of Corifact to rabbits.

A thrombogenicity test was performed in rabbits at doses up to 350 U per kg. Corifact showed no thrombogenic potential at the doses tested.

III. Background

Congenital Factor XIII deficiency is a rare autosomal recessive disease usually associated with a severe bleeding diathesis. Factor XIII (FXIII) after activated by thrombin is an enzyme of the coagulation system that cross-links fibrin. Factor XIII deficiency is the rarest of all factor deficiencies and is also known as Fibrin Stabilizing Factor deficiency diagnosed by coagulation screening tests and detailed family history. The incidence of FXIII deficiency is about 1 in 2-5 million people. Historical data demonstrate that FXIII replacement therapy is the most widely utilized and effective therapy with fresh frozen plasma, cryoprecipitate, or crude factor XIII concentrate from placenta.

CSL Behring has manufactured a novel plasma derived FXIII called Corifact™ approved for orphan designation for congenital FXIII deficiency. CSL Behring proposes an indication for the use of its product human FXIII concentrate, pasteurized, Corifact™ also previously known as Fibrogammin P or P/N, as prophylaxis treatment of FXIII deficiency as a longer acting version than currently marketed products. Corifact™ has a long standing history for clinical use in the EU for over a decade. Common side effects following FXIII therapy include anaphylactic reactions, inhibitor development, thromboembolic events, and rarely transmission of disease. Nevertheless, the benefits of replacement FXIII therapy far outweigh the risks.

IV. Proposed Use and Doses

CSL Behring's Factor XIII concentrate will be administered intravenously as prophylactic therapy at 10-40 U/kg every 4-6 weeks or once a month. The dose and frequency will be determined by treating physician tailored to plasma levels of each patient. The proposed indication is for prophylactic treatment of FXIII deficiency as the half-life for product is longer than other coagulation factors.

V. Recommendation for non-clinical studies

Due to its long-standing history in clinical applications, the safety pharmacology and toxicity of Corifact™ is well established for human use. Based on review of the presented pharmacology and toxicology data, the safety data of Corifact™ in pre-clinical studies appears sufficient to support human use. To note, please monitor for adverse events such as thromboembolic episodes associated with product use.

Due to the potential of immunogenicity associated with all biologic (replacement) therapies, I recommend that the sponsor continue post-marketing monitoring to address immunogenic concerns as this biological product will be administered as a prophylaxis in clinical setting. I also recommend that the sponsor integrates the existing clinical experience and knowledge to address this major safety concern. The sponsor has committed to continued post-marketing monitoring, and completion of on-going clinical trials to address these concerns.

I have no request for any further non-clinical evaluation at this time. There are no outstanding issues preventing this BLA from filing according to FDA guidelines from a pre-clinical standpoint.

VI. General Comments

- No teratogenic, reproductive & developmental toxicity, fertility, mutagenic, secondary pharmacodynamics, genotoxicity or carcinogenic studies were performed using Corifact™ or its predecessors.

- The immunogenicity of treatment with FXIII is a major concern as with all biologics, especially with a prophylactic indication. The sponsor has committed to monitor immunogenicity following FXIII administration such as inhibitor and antibody development in clinical trials and a post-marketing commitment.
- There were no substantial or unexpected adverse events in pre-clinical testing following FXIII administration.

V. List of Non-clinical Studies in STN 125385/0

Study No. (b)(4) 01-00 The Influence of Factor XIII Substitution on bleeding time and clot strength in a FXIII knockout mouse model

Study No. V-692.1 - Factor FXIII from Human Plasma as component of Fibrin Adhesive Effect on Bursting Strength of Rat Skin Wound

Study No. 154-12 - Acute Toxicity Studies in rats with plasma factor FXIII

Study No. B71368 - Fibrogammin P: 14-day intravenous (Bolus) Toxicity Study in the (b)(4) Rat with an Interim Sacrifice after 5 treatments

Study No. 154.24 - Local Toxicity study in rabbits after intravenous, intra-arterial and paravenous injection of BI 71.0123 (plasma factor XIII)

Study No. 154-35 - Safety Pharmacological Investigations with Plasma Factor XIII in (b)(4)- Dogs

Study No. 154-11 - Acute Toxicity studies in mice with plasma Factor XIII

Study No. 154-12 - Acute Toxicity studies in rats with plasma factor XIII

Study No. V-211e - Testing for possible formation of antigenic components through modification of production Procedure

Study No. S10844 – In vivo thrombogenicity test in Rabbit -----(b)(4)-----
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VI. Summary of Non-clinical Studies in STN 125385/0

Study No.	Purpose	Species	Study observations
V-692.1	Efficacy	Rat	Wound healing (tear off assay w/ adhesives)
(b)(4) 01/00	Efficacy	K.O. mice vs. WT (---(b)(4)--- ---)	1.25-200 U/kg; i.v. TEG & bleed time 200 U/kg, n=20/gr.

154-35	Safety Pharmacology	Hemophilia A (b)(4)	1F/1M; 10, 35, 70 U/kg
154-11	Acute (single) dose toxicity	Mouse	N=10 (5M/5F); i.v. saline, 710, 1775, 3550 IU/kg
154-12	Acute (single) dose toxicity	Rat	N=10/gr. (5M/5F) i.v. saline, 71,710, 1420 IU/kg
154-24	Local tolerance	Rabbit	i.v., i.a., p.v. n=3/gr., 250, 71 and 710 IU/kg BW vs. saline
V-211e	Antigenicity	Rabbit/Guinea pig	----- (b)(4) ----- test; passive cutaneous anaphylaxis
S10844	Thrombogenicity	Rabbit	Saline, 35, 100, 350 U/kg i.v.
B71368	Repeat-dose toxicity	rat	N=26 (13M/13F); Saline, 35, 100, 350 U/kg i.v.

----- (b)(4) ----- mouse i.v. = intravenous i.a. = intra-arterial p.v. = paravenous
WT = wildtype gr. = group F=female M=male
----- (b)(4) ----- mouse TEG = thromboelastography BW = body weight
FXIII = Corifact™, human FXIII concentrate, Fibrogammin HS, P or P/N

Primary Pharmacodynamics

Study No. TIM 01/00: The Influence of FXIII Substitution on Bleeding Time and Clot Strength in FXIII Knockout Mouse Model

The purpose of this study was to determine the effect of FXIII administration substitution therapy by investigating the bleeding time (tail tip bleeding) and thromboelastography (TEG) in FXIII knockout (KO) mice (M/F) and wild type mice (----- (b)(4) ----- strain, M/F). The mice (n=20/group) were administered placebo (n=16 WT and n=20 KO mice) or FXIII i.v. at 1.56 (n=7), 3.12 (n=7), 6.25 (n=8), 12.5(n=7), 25 (n=7), 50 (n=4), 100 (n=4), 200 (n=8) U/kg acute dose in KO mice only before TEG determinations were made. Bleeding time was observed following single dose administration of FXIII at 200 IU/kg in KO mice or placebo (WT and KO). KO mice had prolonged bleeding time before administration of FXIII which lead to a dose dependent decrease in bleeding time. Factor XIII activity levels were also noted in this study ranking as follow: (b)(4)-placebo (233%), (b)(4) –placebo (130%), FXIII substituted (up to 122%) and FXIII KO mice (8%).

Study No. V-692.1: Factor XIII from Human Plasma (as component of fibrin adhesive): Effect on Bursting Strength of Rat Skin Wound

The purpose of this study was to test the fibrin adhesive strength of FXIII, human plasma concentrate compared to ----- (b)(4) -----, (20 U/mL, positive control). The

adhesives (0.2 mL) containing increasing amounts of factor XIII (0, 5, 10, 20, 30, 40 IU/mL) were fixed to skin pieces of rat (10/gr./20 skin pieces, 5M/5F) and measure for fixation time after 30 minutes (tear-off assay). -----(b)(4)----- was effective with a dose-dependent increase of tensile strength for FXIII addition to adhesives.

Comment: Differences were observed for FXIII but it did not appear that substantial when compared to control. Also there was a slight decrease noted for 30 U/kg as compared to 20 U/kg dosed groups but these changes were not significant.

Safety Pharmacology

Study No. 154-35: Safety Pharmacological Investigation with plasma factor XIII (BI 71.023) in -(b)(4)- dogs

The objective of this study is to evaluate the safety pharmacology (efficacy) of FXIII in -(b)(4)- (n=2/gr., 1M/1F) following i.v. administration at 62.5, 125, 250 IU/kg for a total of 437.5 IU/kg BW in -----(b)(4)----- dogs. The endpoints examined were circulation and respiratory parameters, serum chemistry panel (hematology and clinical chemistry), clinical observation, coagulation/fibrinolysis parameters.

Platelet numbers drastically declined, then recovered after 15-30 minutes after third treatment of FXIII administration. There was a test article related decrease in pO₂ and pCO₂ transcutaneous levels similar to reference article changes.

Comment: The sample size is too small to make definitive comparisons. There were minor alterations associated with administration of anesthetic drug (----- (b)(4)-----) that are consistent with its predictive adverse events including respiratory changes, and narcosis (lactate build up). However, some alterations are likely test article related including platelets numbers and aggregation being decreased, and slightly to moderately increased albumin/globulin ratio in all animals.

Study No S10844: Fibrogammin P 250: *In vivo* thrombogenicity test in the rabbit (----- (b)(4)-----)

The objective of this study was to quantify thrombogenicity of Fibrogammin P in four doses (saline, 35, 100 and 350 U/kg; -----(b)(4)-----) after i.v. administration to 12 rabbits/F (4 experimental groups, 3 rabbits per group). Thrombus formation was determined and scored using -(b)(4)- method after 10 minutes. The thrombi scores were about the same for all groups tested with no serious alterations between control and test article groups.

Comment: It appears that FXIII does not cause thrombogenic events at any higher rate than that of control animals.

Toxicity

Study No. 154-11: Acute Toxicity study in mice with plasma factor XIII (BI 71.023)

The purpose of this study was to evaluate the toxicity of FXIII i.v. administration in a mice model (n=10/gr., 5M/5F) at acute doses of saline, 710, 1775, or 3550 IU/kg BW. The endpoints evaluated were gross pathology (necropsy, day 15), clinical signs (post-dose 15 min., 1 hr. and daily), BW (Days 1, 2, 8, 15). It appears that test article was well tolerated at all doses and did not present adverse toxicity concerns.

Study No. 154.12: Acute Toxicity study in mice with plasma factor XIII (BI 71.023)

The purpose of this study was to evaluate the toxicity of FXIII i.v. administration in a rat model (n=10/gr., 5M/5F) at acute doses of saline, 71, 710, or 1420 IU/kg BW. The endpoints evaluated were gross pathology (necropsy, day 15), clinical signs (post dose 15 min., 1 hr. and daily), BW (Days 1, 2, 8, & 15). It appears that test article was well tolerated at all doses and did not present adverse toxicity concerns.

Comments: FXIII administration appears to be tolerable in toxicity testing in rodent model creating a safety factor of up to ³ 300X proposed dose, although test groups were too small for statistical analysis.

Study No. B71368: 14-Day intravenous (bolus) toxicity study in -(b)(4)- Rat with an interim sacrifice after 5 treatments

The objective of this study is to evaluate the repeat dose toxicity of FXIII following tail vein i.v. administration at doses for 35, 100, 350 IU/kg/day and saline daily for 14 days in rats (n=10/gr., 5M/5F).

Numerous endpoints and parameters were examined including:

- Clinical observations (daily and immediate pre-and post-dosing)

- Body weight, food consumption

-Organ weight

-Hematology (peripheral blood)

Hematocrit (Hct)

Hemoglobin concentration (Hb)

Erythrocyte count (RBC)

Reticulocyte count (Retic)

Mean cell hemoglobin (MCH)

Mean cell hemoglobin concentration (MCHC)

Mean cell volume (MCV)

Total white cell count (WBC)

Differential WBC count

Neutrophils (N)

Lymphocytes (L)

Eosinophils (E)

Basophils (B)

Monocytes (M)

Large unstained cells (LUC)

Platelet count (Plt)

- Blood Chemistry
 - Alkaline phosphatase (ALP)
 - Alanine aminotransferase (ALT)
 - Aspartate aminotransferase (AST)
 - Total bilirubin (Bili)
 - Urea
 - Creatinine (Creat)
 - Glucose (Gluc)
 - Total cholesterol (Chol)
 - Total protein (Total Prot.)
 - Albumin (Alb)
 - Sodium (Na)
 - Potassium (K)
 - Chloride (Cl)
 - Calcium (Ca)
 - Inorganic phosphorus (Phos)
 - Albumin/Globulin ratio (A/G ratio)
- Ophthalmoscopy
- Urinalysis
- Necropsy-post mortem (Macroscopic pathology, histology, organ weight)
- Cardiovascular parameters
- Toxicokinetics Evaluations (human FXIII and FXIII antigen plasma levels by -(b)(4)-, d= 5, 6, 14, 15)
- Histopathology Analysis

There was a dose-dependent increase in the levels of FXIII and human FXIII antigens in plasma (20-30, 50-150 or 900-3300 mU/mL, respectively). There were changes in clinical biochemistry (including Na⁺, K⁺, Ca²⁺ globulins [males only] and phospholipids [females only]) in the highest dosed group only (350 IU/kg) which are likely treatment related. Increased incidence of thrombosis and fibrosis was observed for high dose group (males only), vasculities in all animals for 100 & 350 IU/kg dosed groups, perivascularitis for higher doses animals (100 & 350 dosed group). These thrombogenic events are likely treatment procedure related (analgesic [-(b)(4)-] and test article) and should be monitored in clinical settings.

Comments: It appears that FXIII is tolerated following repeat administration at 35, 100, and 350 IU/kg in rats resulting in SF of 1. This is further corroborated by long-standing human data and experience with FXIII.

Local Tolerance

Study No. 154.24: Local Toxicity study in rabbits after intravenous, intra-arterial, and paravenous injection of BI 71.0123 (plasma factor XIII)

The purpose of these studies is to evaluate the extent of local tolerance reactions in -----(b)(4)----- rabbits (2 groups, 3M/group with 2 test sites/animal) following

intravenous acute ear vein administration of Fibrogammin P/N (250 IU/kg). The effects were examined based on histopathological, macroscopic (post dose 15 min, 24, 48 and 72 hr) and microscopic alterations (post dose 48 and 72 hours). There were three (3) incidences of slight perivascular hemorrhage (reversible) in test article animals (Day 2) and one instance of perivascular hemorrhage (reversible) in control animal. The results from paravenous and intra-arterial administration were summarized and appear acceptable. FXIII appears to be tolerable.

Comment: The incidence of hemorrhage should be monitored following FXIII administration even though this is an expected side effect from treatment.

Other Toxicity

Study No. V-211e: Factor XIII-concentrate (Fibrogammin HS): testing for possible formation of antigenic components through modification of production procedure

The purpose of this study was to examine the antigenic potential of FXIII variants (commercial vs. FXIII HS, control) in (b)(4)- rabbits (n=10 rabbits, 5M/5F) in the -----(b)(4)-----, Day 29) and passive cutaneous anaphylaxis test in guinea pigs (n=18 test guinea pigs). Two rabbits died during the immunization period due to anaphylactic reactions caused by the for rabbits heterologous antigen (human origin). After immunization, precipitating antibodies against the corresponding antigens could be demonstrated in all rabbits. No precipitating antibodies could be demonstrated after absorption of antisera with antibodies against FXIII-concentrate HS. Passive cutaneous anaphylaxis skin test in guinea pigs (n=18/gr., 2 controls/gr.) following FXIII (commercial vs. FXIII HS) i.v. administration were performed. After both skin tests, the results were similar for control groups to test articles before and after heating step. There were no signs of development of neoantigens.

Comment: It appears that FXIII (commercial vs. FXIII HS) absorption results in similar reactions as compared to controls and one another (formulations).

General Comments on Non-clinical Program: Based on the repeat dose and acute dose toxicity, local tolerance, pharmacodynamics, toxicokinetics, antigenicity, thrombogenicity, and efficacy studies in the pre-clinical program submitted for CSL Behring's FXIII, pasteurized (Corifact) appear adequate to establish an adequate safety profile by addressing potential safety concerns. The findings presented indicate that FXIII (Corifact) is well tolerated with an appropriate safety margin based on proposed clinical dosage. Immunogenicity has been monitored in clinical trials; but continues to be a major concern for prophylaxis indication, thus post marketing monitoring will continue. Pre-clinical and clinical studies have monitored TEG and bleeding time which improved following FXIII administration. Previous clinical experience that has been compiled on FXIII negates the necessity for additional pre-clinical toxicity studies in additional higher order animals as component of preclinical program at this time.

There were additional literature submissions to support Factor XIII concentrate administration including product comparison to recombinant FXIII; factor XIII

administration in sheep; a review article on factor XIII deficiency; and a clinical review on FXIII function.