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sBLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125317/231
CBER Received Date	8/5/2020
PDUFA Goal Date	6/4/2021
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	No
Reviewer Name(s)	Megha Kaushal, MD
Review Completion Date / Stamped Date	May 10, 2021
Supervisory Concurrence	Tejashri Purohit-Sheth, MD
Applicant	CSL Behring GmbH
Established Name	Fibrinogen Concentrate (Human)
(Proposed) Trade Name	RiaSTAP
Pharmacologic Class	Fibrinogen Concentrate
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder as a single dose vial containing 900mg to 1300mg lyophilized fibrinogen concentrate powder for reconstitution
Dosing Regimen	Based on target plasma fibrinogen level: [Target level (mg/dL) - measured level (mg/dL)] 1.7 (mg/dL per mg/kg body weight)
Indication(s) and Intended Population(s)	Acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AA accelerated approval
AC advisory committee
AE adverse event(s)
AUCnorm area under the curve, normalized for actual dose
BE bleeding episode(s)
Cmax maximum plasma concentration
CFD congenital fibrinogen deficiency
CI confidence interval
CL clearance
DVT deep venous thrombosis
EMA European Medicines Agency
FAS full analysis set
FC fibrinogen concentrate
FFP fresh frozen plasma
FRT fibrinogen replacement therapy
GLP good laboratory practices
IDMEAC independent data monitoring and endpoint adjudication committee
ICH intracranial hemorrhage
ITT intention to treat
I.V. intravenous
IVR in vivo recovery
MCF maximum clot firmness
PD pharmacodynamics
PeRC pediatric review committee
PI prescribing information
PK pharmacokinetics
PK-PP pharmacokinetics analysis set
PMR post marketing requirement
PP per protocol
ROTEM rotational thromboelastometry
TEAE treatment emergent adverse event

1. Executive Summary

RiaSTAP, Fibrinogen Concentrate (human) (FCH) was approved under accelerated approval in 2009. RiaSTAP was found to be effective in increasing clot firmness in patients with congenital afibrinogenemia as measured by thromboelastography (TEG). The study showed that RiaSTAP provided a therapeutic benefit as measured by maximum clot firmness (MCF), a pharmacodynamic (PD) measure of fibrinogen, which increased following RiaSTAP administration. The pivotal study, B13023_2001, met its surrogate endpoint of a difference between the pre-infusion (i.e. just before infusion of RiaSTAP) and 1-hour post-infusion MCF values. The study demonstrated that the MCF at 1 hour post-administration of RIASTAP at a dose of 70 mg/kg was higher compared to baseline.

The Applicant provided results from Study BI3023_4003 in this submission as confirmatory evidence in support of an accelerated approval. Study BI3023_4003 is a

multicenter, non-interventional, retrospective cohort study with a prospective observational follow-up period of 12 months to investigate the safety and efficacy of FCH for the treatment of acute bleeding events, routine prophylaxis and perioperative bleeding in subjects with congenital fibrinogen deficiency. The results from 22 subjects in both the retrospective and prospective periods were included in this submission.

During the retrospective period, efficacy assessments were available for 231 acute bleeding events in 15 subjects who were treated with FCH. The hemostatic efficacy was rated by the investigator as effective for 97% of the acute bleeding events. Forty perioperative bleeding events in 14 subjects were treated with FCH and the hemostatic efficacy was rated by the investigator as effective for 97.5% of the perioperative bleeding events. Prophylactic use of FCH in 14 subjects showed a median annualized bleeding rate (ABR) of 1.43.

Similar efficacy results were observed during the prospective period. All 19 acute bleeding events in 7 subjects treated with FCH were rated as effective (100%) by the investigator. All 8 surgical bleeding events in 4 subjects were rated as effective (100%). Six subjects were treated with FCH as routine prophylaxis and the median ABR was 1.26.

Three adverse events (AEs) of special interest occurred in the study: one cephalic vein thrombus, one chronic pulmonary embolus, and one contact dermatitis.

In conclusion, this observational study of retrospective and prospective data had similar efficacy results. Products approved under the accelerated approval regulations, 21 CFR 601.40 - 46, require further adequate and well-controlled confirmatory clinical studies to verify and describe clinical benefit. This supplement fulfills this post marketing requirement to conduct a Phase 4 study B13023_3001 and verifies the clinical benefit.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Subjects were between 2 and 78 years of age.

Table 1 Demographics

	Enrolled Subjects (N=22)
Age	
Mean	34 years
Median	34 years
Sex n (%)	
Female	13 (59.1)
Male	9 (40.9)
Race n (%)	
White	21 (95.5%)
Asian	1 (4.5%)

1.2 Patient Experience Data

N/A

Table 2: Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input checked="" type="checkbox"/>	Clinician-reported outcome	Section 6. 1
<input type="checkbox"/>	Performance outcome	
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting	
<input type="checkbox"/>	FDA Patient Listening Session	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Fibrinogen or Factor I in the human coagulation cascade, is a glycoprotein that in the presence of thrombin forms insoluble fibrin strands which are then cross linked by Factor XIII to form a clot. The three genes coding for fibrinogen, B β (*FGB*), A α (*FGA*) and γ (*FGG*), on chromosome 4 are responsible for the production of A α , B β and γ -polypeptide which polymerize to form insoluble fibrin. Normal fibrinogen level measured by the Clauss method, ranges from 150-350 mg/dL and fibrinogen has a half-life of 3-5 days. The critical plasma fibrinogen level below which hemorrhage usually occurs in patients is approximately 0.5 – 1.0 g/L. In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.

Congenital fibrinogen deficiency is an autosomal recessive disease which includes a group of rare disorders including afibrinogenemia (complete absence or extremely low levels of plasma fibrinogen), hypofibrinogenemia (reduced concentration to ≤ 150 mg/dL), dysfibrinogenemia (dysfunctional fibrinogen) and hypo dysfibrinogenemia (both reduced quantity and quality). The estimated prevalence of afibrinogenemia is approximately 1:1,000,000,² although the prevalence increases in areas of increased consanguinity, and registries in the United Kingdom and Italy show a lower prevalence, approximately 1:6,000,000.³

The clinical manifestation of afibrinogenemia presents with highly variable bleeding phenotypes. Bleeding occurs in 78% of patients with afibrinogenemia, with 10% of the bleeding events being intra-cranial bleeding which is a major cause of death in patients with afibrinogenemia. Neonatal bleeding such as bleeding from the cord stump is usually the presenting event in a majority of patients. Other affected organs are skin, gastrointestinal tract, genitourinary tract, and central nervous system. Menometrorrhagia can occur and first-trimester abortions can occur in afibrinogenemic women, with a 17% incidence of recurrent spontaneous abortions. The frequency of bleeding events (BE) varies from none to multiple episodes per year. The reported frequency of is 0.7 bleeding episodes per year.⁴ The symptoms of hypofibrinogenemia are usually milder. These subjects can be asymptomatic but are at risk for excessive bleeding with trauma.

Of the rare congenital hematological bleeding disorders, congenital afibrinogenemia is associated with the highest risk of thrombosis. These thrombotic events are arterial or venous in nature and occur even in the absence of fibrinogen replacement therapy (FRT).⁵

Management of CFD consists of on-demand treatment of acute bleeding and peri-operative management with FRT. Prophylaxis is occasionally used during pregnancy (to prevent miscarriage or post-partum hemorrhage) and following a life-threatening bleeding event such as intracranial hemorrhage (ICH). FRT is based on achieving target levels of fibrinogen. FRT is the mainstay of treatment of acute bleeding events, perioperative management and in special situations as mentioned for routine prophylaxis.

In the United States, a human fibrinogen concentrate (RiaSTAP®) manufactured by CSLB from pooled plasma was approved by the FDA in 2009 for treatment of acute bleeding episodes in patients with afibrinogenemia and congenital hypofibrinogenemia. In the U.S., besides fibrinogen concentrate (FC), other available sources of fibrinogen for FRT but not approved by the FDA, may be used and these include cryoprecipitate and fresh frozen plasma (FFP). In the U.S. FC remains the most favored form of FRT.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Although FC products were approved in the U.S. for treatment of CFD, the marketing licenses were revoked in 1977 for risks of hepatitis infection and suspected lack of efficacy.⁷ Haemocomplettan® manufactured by CSLB has been approved in European countries since 1985 after improvements in safety and purity.

As stated above, RiaSTAP was approved by the FDA in 2009 for treatment of acute bleeding episodes in patients with afibrinogenemia and congenital hypofibrinogenemia (and approved earlier in Europe under the name Haemocomplettan, as stated above).

Fibryna was approved in 2017. In the U.S., besides fibrinogen concentrate (FC), other available sources of fibrinogen for FRT but not approved by the FDA, may be used and these include cryoprecipitate and fresh frozen plasma (FFP). In the U.S. FC remains the most favored form of FRT.

2.3 Safety and Efficacy of Pharmacologically Related Products

Given in adequate doses, both FFP and cryoprecipitate are effective. Given the low fibrinogen concentration compared to fibrinogen concentrates, FFP and to some extent cryoprecipitate, require larger volume infusions. They also do not have viral inactivation steps and contain additional plasma proteins such as fibronectin, von Willebrand factor, and possible allergens. FFP also carries a risk of transfusion-related acute lung injury (TRALI). The amount of fibrinogen in these products is variable and unknown, and transfusion of multiple units is required. These products also require thawing before use.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

N/A

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Refer to the original BLA submission for further details.

The original approval for RiaSTAP™ BLA 125317 included a post marketing requirement (PMR; Study BI3023_3001) and two post marketing commitments including a study to evaluate the safety and efficacy in the perioperative setting and for routine prophylaxis. (Studies BI3023_4001 and BI3023_4002). On 10/4/2013, CSLB submitted a Good Cause Justification to conduct an alternate post marketing study in place of the originally agreed studies and FDA accepted the justification in a 12/6/13 teleconference. The Agency provided correspondence on 9/9/16, indicating that CSLB is released from the original PMR and two PMCs. These studies were replaced with a new PMR (Study BI3023_4003) intended as the confirmatory trial to verify clinical benefit of RiaSTAP™, given that the original approval was under Accelerated Approval provisions.

2.6 Other Relevant Background Information

N/A

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized and integrated to accommodate the conduct of a complete clinical review without unreasonable difficulty. It was provided electronically and formatted as an electronic Common Technical Document (eCTD) according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies supporting this submission were conducted in compliance with good clinical practice, including appropriate informed consent procedures, and in accordance with acceptable ethical standards.

3.3 Financial Disclosures

Table 3 Financial Disclosures

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request list from applicant)
Total number of investigators identified: <u>11</u>
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>2</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in sponsor of covered study: <u>0</u> Is an attachment provided with details of the disclosable financial interests/arrangements? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>9</u> Is an attachment provided with the reason? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No (Request explanation from applicant)

There were 2 investigators who received grants from the Applicant for their respective bleeding disorders programs at their institution. Given that source document verification

was conducted and that this was a study with retrospective chart review as well as a prospective phase where subjects were observed following treatment with FCH in accordance with institutional practice, any potential bias is likely minimized.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Licensed source plasma is the starting material for isolation of cryoprecipitate. The cryoprecipitate (b) (4) to inhibit the action of (b) (4). Contaminating proteins such as the (b) (4) (b) (4) factors are largely removed by adsorption to Al(OH)₃. A glycine precipitation then eliminates some other proteins. A second Al(OH)₃ adsorption ensures almost complete removal of the (b) (4). The (b) (4) containing the fibrinogen is then stabilized by the addition of (b) (4), followed by heat treatment at 60°C (b) (4) for 20 (b) (4) h to inactivate potentially present viruses. After dilution with buffer, the solution undergoes two more glycine precipitations, and the final precipitate may be stored (b) (4), the precipitate is dissolved, (b) (4) and dialyzed to remove residual (b) (4) followed by filtration and (b) (4). L-arginine monohydrochloride and human albumin are added, and the fibrinogen bulk is sterile-filtered, filled, lyophilized, and capped.

4.2 Assay Validation

The Clauss assay performed in a central laboratory was used to measure baseline and post-infusion plasma fibrinogen activity levels. The analytical validation of the Clauss assay was performed as part of the (b) (4) assay for the manufacturing of the product. For these reasons, additional validation studies for the clinical study were not considered necessary.

4.3 Nonclinical Pharmacology/Toxicology

As per the original BLA, pre-clinical studies were conducted for local tolerance and neoantigenicity (rabbit and guinea pig), acute toxicity (mouse and rat), safety pharmacology/ pharmacodynamics and efficacy ((b) (4) rat sepsis model, porcine coagulopathy model), and pharmacokinetics (non-rodent) at doses ranging from the clinical dose and up to more than ten-fold maximal clinical dose. The safety profile of RiaSTAP™ is sufficient to support BLA approval. There were slight immunogenic responses following RiaSTAP™ administration (dogs and rabbit) likely attributed to immune reaction to human protein which is not atypical with human biologic products. *In vitro* and *in vivo* mutagenesis and carcinogenesis studies have not been performed with RiaSTAP™. Previous experience with fibrinogen indicates a potential for clot formation and thromboembolic events when administered in pre-disposed patients and associated with elevated levels of fibrinogen in plasma. Refer to original BLA review for further details.

4.4 Clinical Pharmacology

Refer to original BLA memo for further details.

A prospective, open label, uncontrolled, multicenter pharmacokinetic study was conducted in the original BLA in 5 females and 9 males with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 8 to 61 years (2 children, 3 adolescents, 9 adults). Each subject received a single intravenous dose of 70 mg/kg RiaSTAP. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion.

No statistically relevant difference was observed between males and females for fibrinogen activity. Subjects less than 16 years of age (n=4) had a shorter half-life (69.9 ± 8.5) and faster clearance (0.73 ± 0.14) compared to subjects >16 years of age. The number of subjects less than 16 years of age in this study limits statistical interpretations.

4.4.1 Mechanism of Action

As above.

4.4.2 Human Pharmacodynamics (PD)

As below.

4.4.3 Human Pharmacokinetics (PK)

The incremental *in vivo* recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 mg/dL (range 1.30 – 2.73 mg/dL) increase per mg/kg. The median *in vivo* recovery indicates that a dose of 70 mg/kg will increase patients' fibrinogen plasma concentration by approximately 120 mg/dL.

The pharmacokinetic analysis using fibrinogen antigen data (ELISA) was concordant with the fibrinogen activity (Claus assay).

4.5 Statistical

There was no formal statistical hypothesis testing applied to this study. Descriptive statistics were used throughout. Data were summarized primarily by treatment of acute bleeding events, treatment and control of perioperative bleeding events, and routine prophylaxis.

4.6 Pharmacovigilance

Routine pharmacovigilance surveillance will be used to identify potential risks.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

Data from Study 4003 were reviewed, as well as the original BLA and related documents. The review focused on hemostatic efficacy in bleeding subjects and the perioperative management of subjects.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

Cover Letter, Financial Disclosure, Clinical Study Report, Case Report Forms.

5.3 Table of Studies/Clinical Trials

Table 4 Clinical Studies

Development Phase	Study Number	Subject Population	Number of Subjects Treated with HFCP
Phase I	BI3.023/ 7MN-101FM	Adults with congenital afibrinogenemia	6 ^c
Phase II	BI3023_2001	Children and adults with congenital fibrinogen deficiency	15
Phase IV	BI3.023/ 7MN-501FM	Children and adults with congenital fibrinogen deficiency	12 ^c
Virus safety	BI3.023/ 7D--402XX-RS	Children and adults with congenital fibrinogen deficiency	6 ^{a, c}
COMP	BI3.023/ 7D-501FM	Children and adults with acquired hypofibrinogenemia	94
Postapproval noninterventional	BI3023_4003 ^b	Children and adults with congenital fibrinogen deficiency	22
Total subjects treated			144 (155)^c

5.4 Consultations

None.

5.4.1 Advisory Committee Meeting (if applicable)

No Advisory Committee (AC) Meeting was conducted for this review. An AC meeting regarding accelerated approval of RiaSTAP was held on January 9, 2009. No issues were identified in this supplement that would benefit from an AC discussion.

5.4.2 External Consults/Collaborations

No external consults/collaborations were needed during this review.

5.5 Literature Reviewed (if applicable)

- 1) Peyvandi F, Bolton-Maggs PH, Batorova A and De Moerloose P. Rare bleeding disorders. *Haemophilia* 2012; 18 Suppl 4: 148-53.
- 2) Lak M, Keihani M, Elahi F, Peyvandi F and Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenemia. *Br J Haematol* 1999; 107: 204-6.
- 3) Peyvandi F, Haertel S, Knaub S and Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. *J Thromb Haemost* 2006; 4: 1634-7.
- 4) Girolami A1, Ruzzon E, Tezza F, Scandellari R, Vettore S, Girolami B. Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. *Haemophilia*. 2006 Jul;12(4):345-51
- 5) Bolton-Maggs, P, Perry D, Chalmers E, Parapia L, Wilde, Williams M, Collins P, Kitchen S, Dolan G, Mumford, A. The rare coagulation disorders – review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. *J Haemophilia* (2004), 10,593-628
- 6) Bornikova L, Peyvandi F, Allen G, Bernstein J, Manco-Johnson MJ. Fibrinogen replacement therapy for congenital fibrinogen deficiency. *J Thromb Haemost* 2011; 9: 1687–1704.

- 7) Rottenstreich A, Lask A, Schliamser L, Zivelin A, Seligsohn U, Kalish Y. Thromboembolic events in patients with severe inherited fibrinogen deficiency. *J Thromb Thrombolysis* (2016) 42:261–266

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

Study BI3023_4003

A Multicenter Study on the Retrospective Safety and Efficacy of Fibrinogen Concentrate (Human) (FCH) for Routine Prophylaxis, Treatment of Bleeding or Surgery in Subjects with Congenital Fibrinogen Deficiency with a Prospective Follow-up Component

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of this study was to retrospectively evaluate the efficacy of FCH in subjects with congenital fibrinogen deficiency.

The secondary objectives of this study were to observe the safety (retrospectively and prospectively) and efficacy (prospectively) of FCH use in subjects who participated in the retrospective portion of the study.

6.1.2 Design Overview

This was a multicenter, non-interventional, retrospective cohort study with a prospective observational follow-up period to investigate the safety and efficacy of FCH for the treatment of acute bleeding events, routine prophylaxis and perioperative bleeding in subjects with congenital fibrinogen deficiency.

All subjects enrolled in the retrospective cohort were expected to participate in the prospective follow-up and evaluation of FCH use and followed for 12 months. The time period for retrospective assessment covered the time period between the first documented use of FCH until the day prior to the prospective period. Subjects were treated at the discretion of the principal investigator (PI) according to current local practice. During the prospective follow-up portion of the study, use of FCH for surgery, treatment of bleeding events and / or routine prophylaxis was captured by either site visits or phone calls approximately every 3 months.

Hemostatic efficacy of FCH for acute bleeding events and / or surgery during both phases of the study were rated by the investigator using a 4-point efficacy scale.

Reviewer Comment:

As congenital fibrinogen deficiency is extremely rare and patients do not bleed frequently, a solely prospective evaluation for the assessment of safety and efficacy would not be feasible as it would entail quite a long evaluation period. Due to this issue, the study was split into the retrospective study and then a prospective period to collect additional data.

6.1.3 Population

The population was based on the eligibility criteria below.
Inclusion criteria:

1. Male or female subjects of any age with a diagnosis of congenital fibrinogen deficiency.
2. Had received FCH (Haemocomplettan P/RiaSTAP) for treatment of bleeding, surgery, or prophylaxis.
3. Written informed consent for study participation obtained before review of retrospective subject records start of prospective observation period, and subjects should be willing and able to adhere to all protocol requirements.

There were no exclusion criteria.

6.1.4 Study Treatments or Agents Mandated by the Protocol

No investigational medicinal product was provided or administered in this non-interventional study.

The study was a review of the historical and prospective use of FCH, with the trade names of Haemocomplettan® P (ex-US product) or RiaSTAP® (US product name). During the prospective portion of the study, subjects were treated with FCH at the discretion of the treating physician / PI and according to the standard of care at the participating study site.

6.1.5 Directions for Use

As above

6.1.6 Sites and Centers

This study was performed as a multicenter study in 2 countries: Canada (8 study sites) and the US (3 study sites)

6.1.7 Surveillance/Monitoring

The following is the schedule of assessments used in the study.

Study Day	Day 1	Retrospective Data Collection ^a	Prospective data Collection	
			Months 3, 6, 9 (±1 mo) ^b	Month 12 / EOS (±1 wk) ^b
Assessment				
Informed consent	X			
Inclusion criteria	X			
Medical / surgical history and demographics		X		
Fibrinogen deficiency history		X		
Assessments associated with FCH use, including bleeding events, surgery or prophylaxis, if available				
Laboratory tests:				
Coagulation ^c		X	X	X
Hematology ^d		X	X	X
Bleeding event (s) with efficacy rating		X	X	X
Surgery with efficacy rating		X	X	X
Prophylaxis regimen		X	X	X
FCH use (log)		X	X	X
Supportive blood products (log)		X	X	X
Concomitant medications ^e		X	X	X
AEs ^f		X	X	X

6.1.8 Endpoints and Criteria for Study Success

Rating	Definition ^a
Excellent	Immediate and complete restoration of hemostasis in the absence of other hemostatic intervention ^b as clinically assessed by the treating physician, and / or < 10% drop in hemoglobin compared to baseline.
Good	Eventual complete restoration of hemostasis in the absence of other hemostatic intervention ^b as clinically assessed by the treating physician; and / or < 20% drop in hemoglobin compared to baseline.
Poor	Incomplete restoration of hemostasis and additional hemostatic intervention ^b required, as clinically assessed by the treating physician; and / or between 20 and 25% drop in hemoglobin compared to baseline.
None	No restoration of hemostasis and alternative hemostatic intervention ^b required, as clinically assessed by the treating physician; and / or > 25% drop in hemoglobin compared to baseline.

CSP = Clinical Study Protocol; FFP = fresh frozen plasma; rFVIIa = recombinant activated factor VII.

^a The assessment considered the clinical condition of the subject, laboratory values such as hematocrit, hemoglobin, and any additional hemostatic treatments, when available.

^b Eg., cryoprecipitate, FFP, rFVIIa.

Reviewer Comment:

The four point scale for hemostatic efficacy in BE has been utilized to assess efficacy for regulatory review of assessment of efficacy outcomes for products that treat coagulation disorders. The limitations of the scale relate to the subjectivity in assessments by the investigator. For example, assessment of cessation of bleeding in soft tissues is measured by pain and in some cases the range of motion. In minor bleeding, it is difficult to elicit substantial improvement in pain and

range of motion that is clinically relevant as the clinical findings may not be associated with severe pain. In addition, there are limitations to the relevance of a drop in hemoglobin to minor bleeding. A drop in hemoglobin is unlikely to be detected with minor bleeding. For these reasons, inclusion of major bleeding and its outcomes are relevant to a robust assessment of hemostatic outcomes when the four point scale is utilized.

6.1.9 Statistical Considerations & Statistical Analysis Plan

There was no formal statistical hypothesis testing applied in this study. Descriptive summary statistics were used throughout. Data were summarized primarily by treatment of acute bleeding events, treatment and control of perioperative bleeding events, and routine prophylaxis.

6.1.10 Study Population and Disposition

Twenty-three subjects were screened, and 22 subjects were enrolled. All 22 subjects completed the study.

6.1.10.1 Populations Enrolled/Analyzed

The key inclusion criteria is as below:

1. Male or female subjects of any age with a diagnosis of congenital fibrinogen deficiency.
2. Had received FCH (Haemocompletan® P or RiaSTAP®) for treatment of bleeding, surgery, or prophylaxis.
3. Written informed consent for study participation obtained before review of retrospective subject records, start of prospective observation period, and willing and able to adhere to all protocol requirements.

There were no specific exclusion criteria.

6.1.10.1.1 Demographics

Subjects were between 2 and 78 years old with a mean age of 34 years. Thirteen of 22 were females (59%). The majority of subjects were white (21; 96%). One subject was Asian.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Of the 22 subjects, 13 had afibrinogenemia, 6 had hypofibrinogenemia and 3 had dysfibrinogenemia.

6.1.10.1.3 Subject Disposition

There were 23 subjects that were screened for inclusion and 22 subjects were enrolled. All subjects had data available for evaluation from both the retrospective and prospective periods. All subjects completed the prospective period.

6.1.11 Efficacy Analyses

The primary efficacy endpoints were based on the investigator's overall assessment of hemostatic efficacy of FCH from a review of the subject's historical records. There were 3 pre-specified primary efficacy endpoints, as related to:

- Treatment of acute bleeding events.
- Treatment and control of perioperative bleeding events.
- Number of bleeding events while on routine prophylaxis.

Reviewer Comment:

Note that the retrospective review period comprised the primary assessment period for efficacy, and the prospective phase was considered secondary.

6.1.11.1 Analyses of Primary Endpoint(s)

Acute Bleeding Events

There were 326 bleeding events during the retrospective period that required treatment. Of these, 231 events in 15 subjects were treated with FCH (27% used RiaSTAP and 73% used Haemocompletan). The mean dose per infusion was 3 g. Among the 160 bleeding events for which information on number of FCH infusions was available, 146 (91%) required only 1 FCH infusion to achieve hemostasis. The majority of bleeds were categorized as traumatic (70%).

During the 12-month prospective period, 15 single bleeding events were observed in 7 subjects (simultaneous bleeding in more than one location had separate efficacy assessments). There were a total of 19 bleeds available for efficacy assessment and all were treated with FCH with a mean dose of 3.9 g. Three of the 7 subjects experienced more than one bleeding event. One subject had 5 bleeding events. The most common type was musculoskeletal bleeds (17/19) and were traumatic in nature. The efficacy assessment was excellent for 18/19 of these events and good in the remaining subject.

Reviewer Comment:

Out of 22 subjects, 15 subjects in the retrospective period had bleeding events. It is expected that the retrospective data collection would have missing data, although it appears that the majority of the bleeds were treated with FCH and most achieved hemostasis after one infusion. The reviewer agrees with these assessments although in some cases, missing elements in data collection resulted in difficulties in interpretation of the data. Nonetheless, it is expected that most bleeds would be traumatic in nature and would resolve after infusion for these minor bleeds. Moreover, the efficacy is further supported with data from the prospective period. The prospective period had less bleeds due to the shorter duration of for this period. The reviewer agrees with the efficacy assessments for the prospective period.

Perioperative Bleeding

During the retrospective period, 14 subjects underwent 53 surgical procedures, but only 40 had efficacy assessments. Of the 40 procedures, 32 (80%) were minor and 8 (20%) were major. Among these, 13 subjects received 82 treatments with FCH (68% with RiaSTAP and 32% with Haemocompletan). The mean dose was 3.4 g and a single infusion was sufficient to achieve hemostasis. The efficacy assessment was excellent in 37 of the 40 procedures (all major surgeries were rated excellent). There was one poor efficacy assessment in a minor surgery.

During the prospective period, there were 8 surgical procedures in 4 subjects. All the procedures were minor and hemostatic efficacy was rated as excellent in 100% of the cases.

Routine Prophylaxis

During the retrospective period, 15 subjects had 119 periods of FCH prophylaxis of varied duration (7 days to 6574 days). The median duration was 860 days with a mean dose of 3.7g. There were a 127 bleeding events that occurred during prophylaxis where the majority achieved hemostasis with one infusion (88%). The median ABR was 1.43 bleeding events per year for FCH prophylaxis.

During the prospective period, 6 subjects had 11 periods of FCH prophylaxis. The median duration was 220 days and mean dose was 3.3 g. There was only 1 bleeding event while on prophylaxis and hemostasis was achieved with one on-demand infusion of FCH. The median ABR was 1.26.

Efficacy for the treatment of bleeding events for the overall period was rated as effective in 97.6% of events with 65.2% events rated as excellent and 32.4% as good.

Reviewer Comment:

The efficacy assessments are reasonable for the perioperative period, as they were all minor surgeries. The median ABR is also reasonable for this population and comparable to other FCH products.

Although there is a paucity of major surgery events, it is likely that FCH in this population would show efficacy, but until there are more robust perioperative data in major surgery, the indication remains limited to treatment of bleeding events. The Applicant has not requested an indication for the perioperative management of bleeding or for routine prophylaxis, only the treatment of acute bleeds.

6.1.11.2 Analyses of Secondary Endpoints

As above (Prospective Period).

6.1.11.3 Subpopulation Analyses

N/A

6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts or discontinuations.

6.1.11.5 Exploratory and Post Hoc Analyses

N/A

6.1.12 Safety Analyses

6.1.12.1 Methods

The secondary objective of this study was to retrospectively and prospectively evaluate the safety of the FCH treatment in a routine clinical setting, based on the reported AEs during both observation periods.

6.1.12.2 Overview of Adverse Events

During the overall period, 65 AEs were reported. The most common AEs were all mild in intensity.

The investigators reported only AEs that they considered related to treatment with FCH in the retrospective period.

Retrospective period-

A total of 9 AEs in 2 subjects were reported. Four of these AEs were respiratory, including events of dyspnea, cough, and wheezing. The remaining events were flushing, venous thrombosis, chest discomfort, chest pain, and vision impairment. All events were reported as non serious. Six were reported as mild, one as moderate, and two as severe. All events resolved.

During the prospective period, 56 AEs were reported in 13 subjects. There were 53 that were reported as not serious and 3 that were serious. None of the AEs were considered related to FCH treatment by the Investigator. The majority (89.3%) were reported as resolved. Study drug was not interrupted in any subject due to an AE and no subjects were withdrawn from FCH treatment.

6.1.12.3 Deaths

There were no deaths during the study.

6.1.12.4 Nonfatal Serious Adverse Events

The three SAEs included 1 head trauma of mild severity, reported as not related and recovered; 1 periorbital cellulitis of moderate severity, reported as not related and recovered; 1 hemoptysis of severe intensity, reported as not related and recovered.

6.1.12.5 Adverse Events of Special Interest (AESI)

Thrombosis and hypersensitivity reactions that are AESIs.

There were three AESI's that were reported. There was one cephalic vein thrombus in the right arm, thought to be related and resolved with anticoagulant. There was one chronic pulmonary emboli, which was severe and related, and one contact dermatitis, mild, not related, and not resolved at the end of study.

Reviewer Comments:

The subject with the cephalic vein thrombosis had dysfibrinogenemia and was pregnant on prophylactic FCH and underwent a c-section. In the post-operative period, four days after her dose of FCH, she developed the thrombosis and treated with anticoagulation. This could be related to FCH, but also could be related to the pro-thrombotic state of pregnancy resulting in thrombosis. The second case of pulmonary embolism had history of three prior PE's and likely dosing of FCH could have exacerbated thrombotic potential leading to this case of PE. The subject was on prophylactic FCH and 5 days after dose had hemoptysis with subsequent PE. She was treated with FCH and heparin. The third case was contact dermatitis of earlobes after ear piercing. This is likely not related to the FCH, and was included as an AESI as it was originally thought to be an IgE mediated hypersensitivity reaction, but was later determined to be a contact dermatitis.

Furthermore, congenital afibrinogenemia represents a group that is at spontaneous risk for paradoxical thrombosis of the arterial and venous type. FRT doses that target 100mg/dL and administered frequently (two to three times in a week) are known to exacerbate the thrombotic risks.

6.1.12.6 Clinical Test Results

Coagulation parameters were collected at isolated timepoints and there were no trends in the data. Baseline coagulation studies demonstrated abnormal coagulation function with decrease to normalization post receipt of study drug. Hematologic parameters collected were within normal limits. Individual subject changes were not analyzed.

Reviewer Comment:

Routine laboratory testing is not considered standard practice with congenital fibrinogen deficiency; however, it is expected that there would abnormal coagulation lab findings with close to normal ranges occurred post administration of the study drug. There is no safety signal noted in review of these laboratory abnormalities.

6.1.12.7 Dropouts and/or Discontinuations

There were no dropouts or discontinuations in the study.

6.1.13 Study Summary and Conclusions

During the overall period, efficacy for treatment of bleeding events was rated as effective in 97.6% of events, perioperative hemostatic efficacy was 100% in major surgeries and 97.5% in minor surgeries, and the median ABR overall was 1.43 in the retrospective period and 1.26 in the prospective period. The efficacy data do show effective treatment with the study drug and is consistent from both the retrospective and prospective periods; however, the non-interventional nature of the study limit robust conclusions. Since a large part of the data is based on historical clinical records, not all relevant data could be collected or were available which complicated the verification and complete certainty of the data provided. Despite these limitations, the prospective data did show hemostatic effectiveness.

During the overall period, 65 AEs were reported in 14 subjects. The most common AEs were all mild in intensity. The 5 severe AEs were visual impairment, severe chest pain, hemoptysis, pulmonary embolism, and pulmonary hypertension. There were 3 SAEs including head trauma, periorbital cellulitis, and hemoptysis. All were not related and subjects recovered without sequelae. The safety profile was favorable and consistent with what was previously observed with this study drug.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

7.1.1 Methods of Integration

This study report includes data from one study, a retrospective cohort study with a prospective observational follow up period. Therefore, there is no integration of data.

7.1.2 Demographics and Baseline Characteristics

N/A

7.1.3 Subject Disposition

N/A

7.1.4 Analysis of Primary Endpoint(s)

N/A

7.1.5 Analysis of Secondary Endpoint(s)

N/A

7.1.6 Other Endpoints

N/A

7.1.7 Subpopulations

N/A

7.1.8 Persistence of Efficacy

N/A

7.1.9 Product-Product Interactions

N/A

7.1.10 Additional Efficacy Issues/Analyses

N/A

7.1.11 Efficacy Conclusions

Efficacy was consistent between the retrospective and prospective periods for the treatment of bleeding events. Efficacy was also observed for perioperative management and routine prophylaxis, although given the limitations of the data for these indications, more robust data will be needed to support these additional indications.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

There were 22 subjects evaluable for safety. This study report includes data from one study. Therefore, there is no integration of data.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The investigators only reported AEs in the retrospective period that they considered related to the treatment of FCH.

8.2.3 Categorization of Adverse Events

N/A

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

N/A

8.4 Safety Results

8.4.1 Deaths

There were no deaths during the study.

8.4.2 Nonfatal Serious Adverse Events

As above; 3 SAEs

8.4.3 Study Dropouts/Discontinuations

There were no dropouts or discontinuations.

8.4.4 Common Adverse Events

As above.

8.4.5 Clinical Test Results

As above.

8.4.6 Systemic Adverse Events

As above.

8.4.7 Local Reactogenicity

As above.

8.4.8 Adverse Events of Special Interest

There were 3 AEs of special interest. One cephalic vein thrombus, one chronic pulmonary emboli, and one contact dermatitis as described above.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

N/A

8.5.2 Time Dependency for Adverse Events

N/A

8.5.3 Product-Demographic Interactions

N/A

8.5.4 Product-Disease Interactions

N/A

8.5.5 Product-Product Interactions

N/A

8.5.6 Human Carcinogenicity

N/A

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.5.8 Immunogenicity (Safety)

N/A

8.5.9 Person-to-Person Transmission, Shedding

N/A

8.6 Safety Conclusions

Refer to Section 6.1.12.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

N/A

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

This product has Orphan designation.

9.1.4 Immunocompromised Patients

N/A

9.1.5 Geriatric Use

N/A

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

N/A

10. CONCLUSIONS

This observational study was intended to gather efficacy and safety data on the use of FCH for the treatment of acute bleeding, routine prophylaxis and use in surgery in subjects with congenital fibrinogen deficiency. This study was intended to serve as the postmarketing requirement confirmatory study pursuant to Accelerated Approval. The study had a retrospective part (collection of historical data corresponding with the subject's first use of FCH) regarding the use of FCH for the treatment of bleeding, routine prophylaxis and use in surgery for subjects with congenital fibrinogen deficiency and a prospective part during which prospective data were collected on the use of FCH for the treatment of acute bleeding, routine prophylaxis and use in surgery.

The data provided in this supplement support hemostatic efficacy for subjects treated with FCH for acute bleeding events. Data were also provided for perioperative and prophylaxis management, which did show achievement of perioperative hemostasis and a low ABR when used prophylactically but were limited. Furthermore, the retrospective nature of the majority of the data presented and non-interventional design of the study make it difficult to draw definitive conclusions regarding the perioperative management of bleeding and routine prophylaxis. There were no new safety signals identified and the safety profile is consistent with what is known for FCH.

This submission fulfills the PMR.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Table 5 Risk Benefit

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> Afibrinogenemia and hypofibrinogenemia are rare. Inadequate functional fibrinogen can cause a potentially fatal bleeding dyscrasia that can begin in infancy and can result in early spontaneous abortions 	<ul style="list-style-type: none"> Afibrinogenemia and hypofibrinogenemia are hereditary disorders that present with life-threatening bleeding
Unmet Medical Need	<ul style="list-style-type: none"> There is a currently licensed fibrinogen derived from pooled human plasma and Fibryna 	<ul style="list-style-type: none"> There is no unmet medical need with the currently licensed products.
Clinical Benefit	<ul style="list-style-type: none"> Efficacy was demonstrated for the treatment of acute bleeds. The limited sample size who received treatment for perioperative management of bleeding during major surgery preclude extending the recommendation to perioperative management. No new safety concerns were identified. 	<ul style="list-style-type: none"> There is evidence for clinical benefit for the treatment of acute bleeding with the caveat that data to support efficacy are based on retrospective data and limited prospective data
Risk	<ul style="list-style-type: none"> The most substantial risks of treatment are thromboembolic events, hypersensitivity reactions and development of anti- fibrinogen antibodies. No antibody development during treatment was reported and there was one hypersensitivity reaction. However, these studies may have been underpowered to adequately identify these potential risks. No other safety signals were apparent. 	<ul style="list-style-type: none"> All the evidence indicates that the risks of Riastap are expected for plasma derived products.
Risk Management	<ul style="list-style-type: none"> The most substantial risks of treatment are thromboembolic events, allergic reactions and development of anti- fibrinogen antibodies. No other safety signals were apparent. 	<ul style="list-style-type: none"> The safety data are limited, however due to the rare nature of this condition, post marketing surveillance will be needed to evaluate the risks of thromboembolism, immunogenicity and hypersensitivity.

11.2 Risk-Benefit Summary and Assessment

Benefits- the efficacy has been established with this confirmatory study for treatment of bleeding events

Risks- Although subjects developed thromboembolic events, this is a known risk of this product and is included in the label to inform physicians that these events have occurred.

11.3 Discussion of Regulatory Options

At the time of original approval, the Applicant was requested to conduct a PMR and two PMC studies including a study to evaluate the safety and efficacy in the perioperative setting and for routine prophylaxis. However, the Applicant submitted a Good Cause letter to the FDA due to significant challenges in enrollment, and FDA agreed to release the PMR and two PMCs. However, the Applicant was required to conduct a PMR study to confirm the clinical benefit. In this submission, the Applicant was able to confirm clinical benefit for the treatment of bleeding. Although data for the perioperative management of bleeding and routine prophylaxis were provided and provide some information on hemostatic efficacy, the data are limited and preclude inclusion of these as specific indications, and the applicant is not seeking these indications at this time.

11.4 Recommendations on Regulatory Actions

This product was approved under accelerated approval regulations, therefore a PMR adequate and well controlled confirmatory clinical study was agreed upon to verify and describe the clinical benefit. It was initially agreed that the study would compare the efficacy of FCH to a historical control. However, due to the rarity of this rare disease population and challenges with enrollment, the Applicant was released from this study and conducted the study presented in this supplement after a Good Cause Letter was sent to the Agency regarding the long duration for a study to be completed and issues with enrollment in this rare population. Due to the challenges with enrollment and limitations with data collection, the Agency agreed to the retrospective and prospective design and collection of data. A randomized control study in this rare patient population would be difficult to complete in a reasonable timeframe. Although this confirmatory study was not the originally intended study, the data provided in this supplement are considered sufficient to confirm benefit for the treatment of acute bleeding. The clinical reviewer recommends approval of this supplement which fulfills the current PMR.

Overall, the product has a favorable benefit/risk assessment and was shown to be safe and efficacious for the treatment of acute bleeding events.

11.5 Labeling Review and Recommendations

The labeling review was ongoing at the completion of this memo. However, key changes included updating Section 6.1 clinical trials experience, addition of pediatric data, and updating Section 14 to include the results of this study.

We generally do not include results for indications that are not included in the *Indications* section of the USPI. However, given the rarity of the disease and anticipated challenges in enrollment of subjects in potential future studies, the review team discussed that the results for perioperative management and routine prophylaxis observed in Study BI3023_4003, albeit limited, would be informative for the healthcare provider. Therefore,

the results for hemostatic efficacy in the perioperative management of bleeding and routine prophylaxis were briefly described in Section 14.

11.6 Recommendations on Postmarketing Actions

No further postmarketing actions are recommended, other than routine pharmacovigilance.