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Division / Office	OTAT
Committee Chair	Megha Kaushal, MD
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Review Completion Date / Stamped Date	
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Applicant	CSL Behring GmbH
Established Name	Fibrinogen Concentrate (Human) (FCH)
(Proposed) Trade Name	RiaSTAP in the US and Canada
Dosage Form(s) and Route(s) of Administration	Single-dose vial containing 900 mg to 1300 mg lyophilized power for solution for intravenous injection
Dosing Regimen	Dose (mg/kg body weight) = [Target level (mg/dL) - measured level (mg/dL)] 1.7 (mg/dL per mg/kg body weight) Dose when fibrinogen level is unknown: 70 mg/kg body weight.
Indication(s) and Intended Population(s)	Treatment of acute bleeding events in children and adults with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia

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GLOSSARY

ABR	Annualized bleeding rate
AE	Adverse Event
AESI	Adverse Event of Special Interest
FDA	Food and Drug Administration
FCH	Fibrinogen Concentrate (Human)
GCP	Good Clinical Practice
IV	Intravenous
Max	Maximum
Min	Minute/Minimum
N	Number of Observations
NA	Not Applicable
PMR	Post Marketing Requirement
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sBLA	supplemental Biologics License Application
SD	Standard Deviation
US	The United States

1. Executive Summary

Fibrinogen concentrate (human) (FCH), under the trade name RiaSTAP, is currently indicated for the treatment of acute bleeding events in subjects with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. CLS Behring submitted this supplemental Biologics License Application (sBLA) to fulfill the post-marketing requirement (PMR) with the results of a multi-center study, BI3023_4003, as RiaSTAP was approved under an accelerated approval process with limited efficacy data.

Study BI3023_4003 was 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 16 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.

I verified the efficacy results for Study BI3023_4003 that appear in the updated label. Based on the available data in this observational study, the statistical evidence supports approval of the applicant’s labelling update on the existing safety and efficacy information.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Congenital afibrinogenemia is a very rare coagulation disorder, usually with an autosomal recessive mode of inheritance. It occurs in about 0.5 to 1 case per million people. Affected people suffer from moderate to severe bleeding after

mild trauma or small surgical interventions. About 54% of afibrinogenemia subjects develop a joint hemorrhage. Hypofibrinogenemia subjects show milder clinical symptoms as their plasma fibrinogen levels generally are above 50 mg/dL.

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

There are currently two approved fibrinogen-concentrate products for congenital fibrinogen deficiency: CSL Behring's HFCP (RiaSTAP) and Octapharma's fibrinogen concentrate Fibryga.

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

FCH was approved under the trade name Haemocomplettan P in nine European countries for both congenital and acquired fibrinogen deficiency and under RiaSTAP in 20 European countries for congenital fibrinogen deficiency only.

FCH was administered in a total of 144 subjects from 4 completed studies, a clinical observational monitoring project (COMP), and Study BI3023_4003.

Table 1: studies in the HFCP clinical development program in congenital fibrinogen deficiency and in the COMP

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]**

COMP = clinical observational monitoring project; HFCP = human fibrinogen concentrate, pasteurized.

Source: Original sBLA125317/231.0; Module 2.5 Clinical overview, p.6.

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

Regulatory history with statistical implications is summarized below.

- On January 16, 2009, FCH was approved under an accelerated approval process with limited efficacy data for the treatment of acute bleeding events in subjects with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
    - At the time of approval, the applicant agreed to one post marketing requirement (PMR; Study BI3023_3001 conducted under IND 13206) to verify the clinical benefit of FCH by comparing hemostatic efficacy with historical control
    - The applicant further agreed to two post marketing commitments (PMCs; Study BI3023_4001 and Study BI2023_4002) to evaluate efficacy and safety of FCH in the perioperative period and routine prophylaxis
- On September 9, 2016, the FDA agreed that the PMR and PMCs would be replaced by a single PMR study (BI3023_4003) to gather additional efficacy 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 would provide the support to convert the accelerated approval to a traditional approval
- On September 28, 2018, the applicant submitted the final study report of Study BI3023_4003 to the FDA under STN 125317/204 but due to work load the FDA was unable to issue a review action by September 28, 2019 and later determined that in order to take action the corresponding labelling updates and supportive datasets should also have been submitted
- On March 20, 2020, to address the missing information, the FDA sent an Information Request for the applicant to submit a prior approval supplement (PAS) Efficacy Supplement, the current amendment

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 SUBMISSION QUALITY AND COMPLETENESS

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

This review memo reports on the completed PMR data submitted under BL 125317/231 as well as the complete study reports, protocols and amendments, and statistical analysis plans (SAPs) submitted under BL 125317/204.

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

1. Labelling Supplement BLA 125317/231.0

   a. Module 1.14 Labelling
   b. Module 2.5 Clinical Overview
   c. Module 2.7 Clinical Summary
   d. Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies: Analysis Datasets
2. Labelling Supplement BLA 125317/231.2
   a. Module 1.11.3 Efficacy Information Amendment
3. Labelling Supplement BLA 125317/231.6
   a. Module 1.11.3 Efficacy Information Amendment
4. Labelling Supplement BLA 125317/231.7
   a. Module 1.14 Labelling
5. Supplement BLA 125317/204.0
   a. Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies: Synopsis, Report Body, Protocols, and SAPs

5.3 Table of Studies/Clinical Trials

Only one clinical study was submitted in support of this submission. See Table 2 for the study overview.

Table 2: Overview of Study BI3023_4003

Study	No. Subjects Treated	Study Title and Design	Treatment	Study Timeframe
BI3023_4003	22	"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" Retrospective, multicenter cohort study with a prospective component; treatment with FCH and all laboratory tests were in the scope of routine therapeutic procedures. Efficacy variables: laboratory measures of fibrinogen levels and physician's assessment of hemostasis efficacy.	Therapeutic (acute bleeding events and during surgery) and prophylactic treatment as part of routine clinical practice and not mandated by a clinical study protocol.	May 2015 to December 2017

Source: Original sBLA125317/231.0; Module 2.5 Clinical overview, p.9.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Study BI3023_4003

The protocol for study BI3023_4003 is titled "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)

Primary objective:

- To retrospectively observe the efficacy of FCH in subjects with congenital fibrinogen deficiency

Secondary objective:

- 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 is 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. Subjects were enrolled in the retrospective portion of the study and prospectively followed for 12 months for evaluation of FCH use. During the prospective period, data on FCH use were collected every 3 months.

6.1.3 Population

Selected inclusion criteria:

1. Male or female subjects of any age with a diagnosis of congenital fibrinogen deficiency
2. Had received FCH (Haemocomplettan P or RiaSTAP) for treatment of bleeding, surgery or prophylaxis
3. Written informed consent given and willing and able to adhere to all protocol requirements

6.1.4 Study Treatments or Agents Mandated by the Protocol

No investigational product was administered. Subjects who used FCH with the trade names of Haemocomplettan P or RiaSTAP were enrolled retrospectively and followed prospectively. During the prospective portion of the study, subjects were treated with FCH at the discretion of the treating physicians according to the standard of care at each study site.

6.1.6 Sites and Centers

The study included eight sites in Canada and three sites in the US.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint: Investigator's overall assessment of hemostatic efficacy of FCH from review of historical records in:

- Treatment of acute bleeding episodes according to the defined efficacy scale in Table 3. Treatment of bleeding episodes was classified as effective if the efficacy rating was excellent or good and ineffective if the efficacy rating was poor or none.
- Treatment and control of perioperative bleeding episodes according to the defined efficacy scale in Table 4. Treatment of perioperative bleeding episodes was classified as effective if the efficacy rating was excellent or good and ineffective if otherwise.

- The number of bleeding episodes while on prophylaxis. Routine prophylaxis was defined as fibrinogen use with a meaningful dose frequency for at least 3 days.

Secondary Endpoints:

- Reported AEs during both the retrospective and prospective periods
- Investigator's overall assessment of the hemostatic efficacy of FCH during the prospective period in:
    - Treatment of acute bleeding episodes according to the defined efficacy scale in Table 3
    - Treatment and control of perioperative bleeding episodes according to the defined efficacy scale in Table 4
    - The number of bleeding episodes while on prophylaxis

Table 3: Treatment of acute bleeding episodes: Rating of Hemostatic Efficacy

Rating	Definition[1]
Excellent	Immediate and complete restoration of hemostasis in the absence of other hemostatic intervention[2] 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[2] 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[2] 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[2] required, as clinically assessed by the treating physician; and / or >25% drop in hemoglobin compared to baseline

1 The assessment will consider the clinical condition of the subject, laboratory values such as haematocrit, hemoglobin, and any additional hemostatic treatments, when available.
2 e.g. cryoprecipitate, FFP, rFVIIa

Source: Original sBLA125317/204; Module 5.3.5.2 US Protocol v1. 0 Amendment No. 2, p.40

Table 4: Treatment and control of perioperative bleeding episodes: Rating of hemostatic efficacy

Rating	Definition[1]
Excellent	Hemostasis clinically not significantly different from normal (e.g., achieved hemostasis comparable to that expected during similar, surgery in a non factor-deficient patient) in the absence of other hemostatic intervention[2]
Good	Normal or mildly abnormal hemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to hemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other hemostatic intervention[2]
Poor	Moderately abnormal hemostasis in terms of quantity and/or quality (e.g., moderate hemorrhage that is difficult to control) and/or additional hemostatic intervention[2] required
None	Severely abnormal hemostasis in terms of quantity and/or quality (e.g., severe hemorrhage that is difficult to control) and/or additional hemostatic intervention[2] required

1 The assessment is to include the entire period from the start of the surgical procedure until hemostasis is secured and wound healing is adequate, up to a maximum of 6 weeks after the procedure. The assessment will consider the clinical condition of the subject, laboratory values such as haematocrit, hemoglobin and any additional hemostatic treatments, when available.
2 E.g., cryoprecipitate, FFP, rFVIIa

Source: Original sBLA125317/204; Module 5.3.5.2 US Protocol v1. 0 Amendment No. 2, p.41.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size Estimation
Approximately 20 subjects were planned. It was not based on statistical power considerations.

Analysis Populations

- Enrolled population: all subjects who either provided written informed consent or had a consent waiver obtained to participate in the study
- Safety population (retrospective period): all enrolled subjects with documented use of FCH
- Prospective follow-up population: all subjects in the safety population who provide at least one data point for the prospective follow-up period

Statistical Methods
Descriptive statistics were used. Continuous variables were summarized in terms of mean, standard deviation (SD), median, minimum (min) and maximum (max). Categorical variables were summarized using frequency counts and percentages.

Primary Efficacy Endpoints:
Treatment of acute bleeding episodes
The investigator's overall assessments of the bleeding episodes were summarized. The proportion of bleeding episodes classified as effective was also presented.

Treatment and control of perioperative bleeding episodes
The investigator's overall assessments of the perioperative bleeding episodes were summarized descriptively. The proportion of perioperative bleeding episodes classified as effective was also presented.

Annualized bleeding rate during prophylaxis
The number of bleeding episodes (annualized) while on prophylaxis and the number of days on treatments were summarized descriptively. The annualized bleeding rate (ABR) per subject was calculated as below:

$$ABR = \frac{Number\ of\ treated\ bleeding\ episodes}{Duration\ of\ treatment\ period\ (days)} * 365.25$$

Secondary efficacy endpoints:
The investigator's overall assessments of hemostatic efficacy of FCH during the prospective period were analyzed using the same methods as the respective primary efficacy endpoints.

Safety Endpoints:
Adverse events (AEs)
AEs were counted and grouped by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities. Incidence and incidence rates were calculated.

Handling of Missing Data
Observations with missing efficacy assessments were excluded from the analyses. If the start date of a bleeding episode was incomplete or missing completely and it was impossible to determine whether the bleeding episode occurred during routine prophylaxis periods, the bleeding episode was not counted.

No imputation of missing values was performed unless indicated otherwise:

- No imputation was used for dates including date of informed consent, date of eligibility, date of birth, date of follow-up visit, and date of subject's last visit
- Incomplete or missing treatment date:
  - Missing start date: impute as 1st of the month
  - Missing start date and month: no imputation
  - Missing end date: impute as the last date of the month
  - Missing end date and month: no imputation
- Incomplete or missing AE date:
  - Missing start date: impute as the 1st of the month; if month and year were the same as the first treatment date, impute as the first treatment start date

- Missing start date and month: impute as the date of first treatment if it was the same year as the first treatment date; impute as January 1st if a later year; impute as December 31 if it was an earlier year
- Missing end date and not ongoing: impute as the last date of the month
- Missing end date and month and not ongoing: impute as the last recorded visit date if the year was the same as the last recorded visit date; impute as December 31 if it was an earlier year

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 5 provides the sample sizes of the analysis populations for the retrospective and the prospective periods. Twenty-two subjects were enrolled retrospectively. All subjects completed the prospective follow-up. Thus, all 22 subjects were included in the enrolled and safety populations.

Table 5: Summary of Subject Disposition

	Subjects Overall (N= 22)
Characteristics	**n**
Enrolled	22
Retrospective period	22
Prospective period	22
Completed the study	22
Did not complete the study	0

n = number of subjects.

Source: Original sBLA125317/204; Module 5.3.5.2 Clinical Study Report, p.33

6.1.10.1.1 Demographics

All the enrolled subjects were between 2 and 79 years old with a mean age of 34 years old. Thirteen subjects (59%) were females, 21 (95.5%) were white and 1 (4.5%) was Asian. There were many missing values in height, weight and BMI. Only four subjects had information on BMI. See Table 6.

Table 6: Demographic and baseline characteristics for enrolled population.

Characteristic	Statistic	Enrolled Subjects (N = 22)
Age at enrolment (years)	Mean (SD)	34.0 (24.4)
	Median (min; max)	34.0 (2; 78)
Sex		
Male	N (%)	9 (40.9)
Female	N (%)	13 (59.1)
Ethnicity		
Not Hispanic or Latino	N (%)	20 (90.9)
Hispanic or Latino	N (%)	2 (9.1)
Race		
White	N (%)	21 (95.5)
Asian	N (%)	1 (4.5)
Height (cm)	n	4
	Mean (SD)	107.4 (56.2)
	Median (min; max)	97.3 (52; 183)
Weight (kg)	n	7
	Mean (SD)	31.2 (36.9)
	Median (min; max)	12.3 (3.5; 86.0)
BMI (kg/m^2)	n	4
	Mean (SD)	17.1 (4.4)
	Median (min; max)	16.1 (12.9; 23.3)
BMI categories (kg/m^2):	n	4
< 18.5	n (%)	3 (75.0)
18.5 - 24.9	n (%)	1 (25.0)
25.0 - 29.9	n (%)	0
≥ 30	n (%)	0

N: number of subjects, n: number of subjects with assessed characteristic. BMI: Body Mass Index

Source: Original sBLA125317/204; Module 5.3.5.2 Clinical Study Report, p.34

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Of the 22 subjects, 13 had a history of afibrinogenemia, 6 hypofibrinogenemia and 3 dysfibrinogenemia. Eighteen subjects had prior or concomitant diseases and nine had surgical procedures before the first dose of FCH.

6.1.10.1.3 Subject Disposition

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

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Treatment of acute bleeding episodes

Table 7 shows the characteristics of bleeding events. During the retrospective period, 17 of the 22 subjects experienced 336 treated bleeding events. Out of 336, 250 (74.4%) bleeding events in 16 subjects were treated with FCH. Among the 250 bleeding events treated with FCH, 32 bleeding events (12.8%) were spontaneous, 175 (70.0%) were traumatic, 6 (2.4%) were post-operative, and 37 (14.8%) were unknown. This distribution was similar among all the 336 treated bleeding events, where 44 (13.1%) were spontaneous, 236 (69.8%) were traumatic, 6 (1.8%) were post-operative, and 50 (14.9%) unknown.

Efficacy assessments were available for 314 bleeding events and for 231 bleeding events treated with FCH. Among the 231 bleeding events, 158 (68.4%) were rated as excellent, 66 (28.6%) as good, 4 (1.7%) as poor, 3 (1.3%) as none. Therefore, FCH treatments showed a 97.0% effective rate. For the 83 bleeding events not treated with FCH, the effective rate was 98.8%.

Table 7: Characteristics of bleeding events during retrospective period. When counting the number and nature of treated bleeding events, only unique bleeding events were counted.

Characteristics	FCH treatments	Other treatments	All treatments
Number of subjects with treated bleeding events	16	7	17[a]
Nature of bleeding events[b] [n (%)]			
N	250	86	336
Spontaneous	32 (12.8)	12 (14.0)	44 (13.1)
Traumatic	175 (70.0)	61 (70.9)	236 (69.8)
Post-surgery	6 (2.4)	0 (0)	6 (1.8)
Unknown	37 (14.8)	13 (15.1)	50 (14.9)
Investigator's overall efficacy assessment[c] [n (%)]			
N (missing)	37	4	41
N (observed)	231	83	314
Excellent	158 (68.4)	41 (49.4)	199 (63.4)
Good	66 (28.6)	41 (49.4)	107 (34.1)
Poor	4 (1.7)	1 (1.2)	4 (1.3)
None	3 (1.3)	0 (0)	4 (1.3)
Effective* (excellent and good)	224 (97.0)	82 (98.8)	306 (97.5)

* Based on bleeding events with observed efficacy assessments;
FCH=Fibrinogen concentrate, human.
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, pgs.52-54
[a] Subjects could be treated with multiple types of concentrate.
[b c] Total number of bleeding events with efficacy assessments might not be equal to total number of bleeding events by nature because multiple entries in the case report form (CRF) with the same start date and the same nature of bleeding were considered as one unique bleeding event. Subjects could have multiple treated injuries during the same bleeding event that contribute to efficacy assessment evaluation.

Reviewer Comment:
Efficacy evaluation was based on bleeding events with observed efficacy assessments. The applicant reported an effective rate of 97.0% for FCH treatment but the rate was calculated excluding the 37 observations with missing efficacy assessments. Thus, the reported efficacy result could be biased due to missing data If we assume all the observations with missing efficacy assessments as ineffective, the effective rate would be 83.6% for FCH and 94.3% for other treatments.

Treatment and control of perioperative bleeding episodes

Table 8 summarizes the perioperative assessment of hemostasis. During the retrospective period, 16 subjects had 64 surgical procedures of which 53 had hemostatic efficacy assessed. FCH was more commonly administered than other treatments. Forty-two (65.6%) surgical procedures were treated with FCH and 40 had efficacy assessments. Of the 40 surgical procedures, 32 (80%) were minor, 8 (20.0%) were major. The overall efficacy assessments were excellent in 37 (92.5%), good in 2 (5.0%), and poor in 1 (2.5%). For the 13 surgical procedures not treated with FCH, the effective rate was 100%.

Table 8: Perioperative assessment of hemostasis during retrospective period.

Characteristics	FCH treatments	Other treatments	All treatments
Number of subjects with surgical procedures	14	8	16[a]
Number of surgical procedures	42	22	64
Number of subjects with efficacy assessment during surgery	14	4	16
Number of efficacy assessments during surgery	40	13	53
Type of surgery [n (%)]			
Major	8 (20.0)	4 (30.8)	12 (22.6)
Minor	32 (80.0)	8 (61.5)	40 (75.5)
Unknown	0 (0)	1 (7.7)	1 (1.9)
Investigator's overall efficacy assessment [n (%)]			
Excellent	37 (92.5)	13 (100)	50 (94.3)
Good	2 (5.0)	0 (0)	2 (3.8)
Poor	1 (2.5)	0 (0)	1 (1.9)
None	0 (0)	0 (0)	0 (0)
Effective* (excellent and good)	39 (97.5)	13 (100)	52 (98.1)

*Based on bleeding events with observed efficacy assessments;
FCH=Fibrinogen concentrate, human.
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, pgs.56-57
[a] Subjects could be treated with multiple types of concentrate.

Annualized bleeding rate during prophylaxis

Table 9 summarizes bleeding events during routine prophylaxis. During the retrospective period, 15 subjects were treated with routine prophylaxis with FCH. The median number of days on routine prophylaxis was 860 days, with a minimum of 7 days and a maximum of 6574 days. Among the 14 subjects with available data, the mean and the median ABR were 5.71 and 1.43, respectively. One subject with incomplete start and stop date was excluded from per subject ABR calculation.

Table 9: Summary of routine prophylaxis with FCH during retrospective period

Characteristics	Retrospective
Per-subject ABR	
N	14
Mean (SD)	5.71 (13.79)
Median	1.43
Min, Max	0, 52.18
Total number of days in treatment period	
N	15
Mean (SD)	1766.5 (2048.3)
Median	860.0
Min, Max	7, 6574

ABR: annualized bleeding rate; FCH=Fibrinogen concentrate, human.
Per subject ABR is defined as (number of treated bleeding events during the treatment period) / (duration of treatment period in days/365.25)
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, p.58

6.1.11.2 Analyses of Secondary Endpoints

Treatment of acute bleeding episodes

See Table 10 for the characteristics of bleeding events during the prospective period. During the prospective period, 7 of the 22 subjects experienced 15 unique bleeding events that required treatment and 14 of them were treated with FCH. Among the 14 treated bleeding events, 2 (14.3%) were spontaneous, 11 (78.6%) were traumatic and 1 (7.1%) was post-operative. Efficacy assessments were available for 19 bleeding events in the 7 subjects and all bleeding events were treated with FCH. Bleeding events of different location but of the same nature and of the same date were considered as a single bleeding event. However, efficacy could be assessed separately by location, therefore yielding more bleeding events for which efficacy assessment was available. Among the 19 treated bleeding events, 18 (94.7%) was rated as excellent and 1 (5.3%) as good. Overall, FCH treatments showed an effective rate of 100% during the prospective period.

Table 10: Characteristics of bleeding events during prospective period. When counting the number and nature of treated bleeding events, only unique bleeding events were counted.

Characteristics	FCH treatments	Other treatments	All treatments
Number of subjects with treated bleeding events	7	1	7[a]
Nature of bleeding events[b] [n (%)]			
N	14	1	15
Spontaneous	2 (14.3)	0	2 (13.3)
Traumatic	11 (78.6)	0	11 (73.3)
Post-surgery	1 (7.1)	1 (100)	2 (13.3)
Unknown	0 (0)	0	0 (0)
Investigator's overall efficacy assessment[c] [n (%)]			
N (missing)	0	1	1
N (observed)	19	0	19
Excellent	18 (94.7)	NA	18 (94.7)
Good	1 (5.3)	NA	1 (5.3)
Poor	0 (0)	NA	0 (0)
None	0 (0)	NA	0 (0)
Effective* (excellent and good)	19 (100)	NA	19 (100)

* Based on bleeding events with observed efficacy assessments; NA=not applicable; FCH=Fibrinogen concentrate, human.
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, pgs.61-63
[a] Subjects could be treated with multiple types of concentrate.
[b c] Total number of bleeding events with efficacy assessments might not be equal to total number of bleeding events by nature because multiple entries in the case report form (CRF) with the same start date and the same nature of bleeding were considered as one unique bleeding event but subjects could have multiple treated injuries during the same bleeding event that contribute to efficacy assessment evaluation.

Treatment and control of perioperative bleeding episodes

Table 11 shows the summary of the perioperative assessment of hemostasis during surgery. During the prospective period, 5 subjects had 9 surgical procedures. Eight of the 9 surgical procedures were treated with FCH. All the 8 surgical procedures were considered as minor surgeries. The rating of hemostatic efficacy was rated as excellent in all 9 surgical procedures. Overall, the FCH treatments of perioperative bleeding showed an effective rate of 100% during the prospective period.

Table 11: Perioperative assessment of hemostasis during prospective period.

Characteristics	FCH treatments	Other treatments	All treatments
Number of subjects with surgical procedures	4	1	5
Number of surgical procedures	8	1	9
Number of subjects with efficacy assessment during surgery	4	1	5
Number of efficacy assessments during surgery	8	1	9
Type of surgery [n (%)]			
Major	0	0	0
Minor	8 (100)	1 (100)	9 (100)
Unknown	0	0	0
Investigator's overall efficacy assessment* [n (%)]			
Excellent	8 (100)	1 (100)	9 (100)
Good	0	0	0
Poor	0	0	0
None	0	0	0
Effective* (excellent and good)	8 (100)	1 (100)	9 (100)

* Based on bleeding events with observed efficacy assessments;
FCH=Fibrinogen concentrate, human.
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, pgs.64-65

Annualized bleeding rate during prophylaxis

See Table 12 for the results on routine prophylaxis. During the prospective period, six subjects were treated with FCH as routine prophylaxis. The median number of days on routine prophylaxis was 220 days, with a minimum of 128 days and a maximum of 340 days. The mean and the median ABR were 1.21 and 1.26, respectively.

Table 12: Summary of routine prophylaxis with FCH during the prospective period

Characteristics	Prospective period
Per-subject ABR	
N	6
Mean (SD)	1.21 (1.09)
Median	1.26
Min, Max	0, 2.77
Total number of days in treatment period	
N	6
Mean (SD)	227.3 (93.0)
Median	220.0
Min, Max	128.0, 340.0

ABR: annualized bleeding rate; FCH=Fibrinogen concentrate, human.
Per subject ABR is defined as (number of treated bleeding events during the treatment period) / (duration of treatment period in days/365.25)
Source: Adapted sBLA125317/204; Module 5.3.5.2 Clinical Study Report, p.66

6.1.11.3 Subpopulation Analyses

Because 21 of the 22 enrolled subjects were white and 1 was Asian, group analyses by race was not informative. During the retrospective period, the FCH treatments of acute bleeding episodes showed an effective rate of 95.9% for males and of 100% for females. For perioperative bleeding episodes, the effective rate was 100% for males and 93.8% for females. Six males and eight females were treated with FCH as routine prophylaxis. The median ABR was 2.27 for males and 0.70 for females.

During the prospective period, the effective rates for acute bleeding episodes and perioperative bleeding episodes were 100% for both males and females. Three males and three females were treated with FCH as routine prophylaxis. The median ABR was 0 for males and 1.44 for females.

Among the 22 subjects, 13 subjects had afibrinogenemia, 6 hypofibrinogenemia and 3 dysfibrinogenemia. Because subjects with afibrinogenemia have more severe clinical symptoms due to lack of fibrinogen, most of the bleeding episodes analyzed for efficacy were from subjects with afibrinogenemia. During the retrospective period, of the 231 acute bleeding episodes treated with FCH and with efficacy assessments, only 2 were from subjects with hypofibrinogenemia

and 0 from subjects with dysfibrinogenemia. The FCH treatments of acute bleeding episodes had an effective rate of 97.4% for afibrinogenemia and of 100% for hypofibrinogenemia. Among the 40 perioperative bleeding events, 26 were from subjects with afibrinogenemia, 7 from hypofibrinogenemia, and 7 from dysfibrinogenemia. The FCH treatments of perioperative bleeding events had an effective rate of 96.2% for afibrinogenemia, 100% for both hypofibrinogenemia and dysfibrinogenemia. Twelve afibrinogenemia and only two hypofibrinogenemia subjects were treated with FCH as routine prophylaxis. The median ABR was 1.88 for afibrinogenemia and 0 for hypofibrinogenemia.

During the prospective period, all acute bleeding episodes treated with FCH were from subjects with afibrinogenemia and the effective rate was 100%. Among the 8 perioperative bleeding events treated with FCH, 3 were from subjects with afibrinogenemia and 5 from subjects with dysfibrinogenemia and the effective rates were 100% for both. The six subjects who were treated with FCH as routine prophylaxis were all afibrinogenemia.

6.1.11.4 Dropouts and/or Discontinuations

All 22 subjects completed the study. However, retrospective data were analyzed as recorded in the database. Efficacy assessments were evaluated based on observed cases only with missing data being ignored. If we assume all the observations with missing efficacy assessments as ineffective during the retrospective period, the FCH's effective rate for treatment of acute bleeding episodes would be 83.6%, instead of 97.0%.

6.1.12 Safety Analyses

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

There were three serious adverse events (SAEs): one head trauma of mild severity, reported as not related and recovered; one periorbital cellulitis of moderate severity, reported as not related and recovered; one hemoptysis of severe intensity, reported as not related and recovered. All three SAEs occurred during the prospective period.

6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events that are of special interest include thromboembolic events and hypersensitivity. There were three AEs of special interest in three subjects: one cephalic vein thrombus in the right arm which was considered mild and related to FCH and resolved with anticoagulant; one chronic pulmonary emboli which was considered severe, reported as not related to FCH and had unknown outcome; one contact dermatitis which was considered mild, not related to FCH and was not resolved at the end of the study. The vein thrombus occurred during the

retrospective period and the other two AESIs occurred during the prospective period.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

Study BI3023_4003 was 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. A total of 22 subjects were enrolled in the study.

During the retrospective period, efficacy assessments were available for 231 acute bleeding events in 16 subjects who were treated with FCH. The FCH treatments had an effective rate of 97% based on the acute bleeding events with efficacy assessment. In addition, FCH treatments showed an effective rate of 97.5% based on 40 perioperative bleeding events with efficacy assessment. Prophylactic use of FCH in 14 subjects showed a median ABR of 1.43.

The efficacy results were consistent during the prospective period. All 19 acute bleeding events in 7 subjects treated with FCH were rated as effective (100%) by the investigators. All 8 surgical bleeding events were rated as effective (100%). Prophylactic use of FCH in 6 subjects showed a median ABR of 1.26.

The study had three AESIs in three subjects: one cephalic vein thrombus, one chronic pulmonary embolus, and one contact dermatitis.

10.2 Conclusions and Recommendations

Because the study was an observational study and efficacy assessments during the retrospective period were based on observed cases, the efficacy results could be affected by missing data. However, since similar efficacy results were observed in the prospective period, I recommend approval of the applicant's labelling update on the existing safety and efficacy information.