Application Type	Original BLA
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Committee Chair	Ze Peng, Ph.D.
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Priority Review	No
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Review Completion Date / Stamped Date	
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Applicant	OCTAPHARMA
Established Name	HUMAN FIBRINOGEN
(Proposed) Trade Name	FIBRYNA
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	A sterile, lyophilized powder for reconstitution for intravenous injection.
Dosing Regimen	70 mg/kg body weight for unknown fibrinogen level. Recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding or minor surgery and 150 mg/dL for major bleeding or major surgery.
Indication(s) and Intended Population(s)	For the treatment of acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

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GLOSSARY

AUC	Area under Curve
BE	Bleeding Episode
BLA	Biologics License Application
BW	Body Weight
BMI	Body Mass Index
CI	Confidence Interval
eCTD	electronic Common Technical Document
EDR	Electronic Document Room
FDA	Food and Drug Administration
IA	Interim Analysis
IDMEAC	Independent Data Monitoring & Endpoint Adjudication Committee
ITT	Intention-to-treat
MCF	Maximum clot firmness
PK	Pharmacokinetic
SD	Standard Deviation
TEG	thromboelastography

1. Executive Summary

This Biologics License Application (BLA) for the approval of a human fibrinogen concentrate, FIBRYNA, proposes an indication for the treatment of acute bleeding episodes (BEs) (b) (4) in adult and pediatric subjects with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

The primary evidence is based on the results from a planned interim analysis (IA) of the pivotal study FORMA-02: a prospective, open-label, uncontrolled, phase 3 study to assess the efficacy and safety of FIBRYNA for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency. The primary efficacy endpoint for acute bleeding was the proportion of subjects with a treatment success for treated first BEs. A treatment success was defined as hemostatic efficacy rating of excellent or good by the investigator. Please refer to Section 6.1.8 for more details.

The submission included data from 13 subjects from FORMA-02, 11 of whom were treated for at least one acute subjects. There were 23 BEs in total, and 11 first BEs for these 11 subjects. Nine of the 11 first BEs were rated as excellent and 2 were rated as good according to the assessment of the investigator. The proportion of treatment success for the first BEs was 100% (11/11) and the 90% confidence interval (CI) was 80% to 100%.

One subject, (b) (6) , was identified by the clinical reviewer to be excluded from the final analysis. This subject was under-dosed by ½ the dose and did not experience an increase in fibrinogen level at 1 and 3 hours post dose, but both the investigator and IDMEAC rated the hemostatic efficacy as excellent. Since it is questionable whether the hemostasis efficacy was attributable to the product, a sensitivity analysis removed this subject from the FAS dataset.

The success rate remains unchanged at 100% (10/10), but the lower bound of the CI decreases to 77.76%, and the pre-specified success criterion is still met. The total number of BEs is changed to 22 in this sensitivity analysis.

Surgical prophylaxis was assessed for four surgical procedures in four subjects; three procedures were classified as minor and one was classified as major. All four of these surgeries were rated as excellent or good by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC), so the overall success rate was 100%.

The safety evaluation revealed that no subject reported inhibitory effects. No subjects developed anti-fibrinogen antibodies during the study.

No statistical issues were identified during the review of this application. I confirmed that the primary efficacy endpoint analysis provides statistical evidence to support the effectiveness of the product in the proposed indication.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Congenital fibrinogen deficiency is an inherited coagulation disorder with considerably higher incidence in consanguineous marriages. Conditions of congenital fibrinogen deficiency include afibrinogenaemia (complete absence of plasma fibrinogen), hypofibrinogenaemia (reduced concentration of plasma fibrinogen) and dysfibrinogenaemia (presence of abnormal or dysfunctional fibrinogen). Affected individuals with afibrinogenaemia have a highly variable bleeding tendency that can be severe, including life-threatening bleeding and spontaneous/trauma-related bleeds. Afibrinogenaemia has an estimated prevalence of around 1:1,000,000. Fibrinogen concentrate preparations are the basis for the treatment of hemorrhages in patients with congenital fibrinogen deficiency and show advantages over plasma and cryoprecipitate therapeutic options per the published papers in 2010[1] and 2011[2]. The available evidence in the published articles in 2009[3] suggests that fibrinogen concentrates are well tolerated and can rapidly and safely restore hemostasis in patients with fibrinogen deficiencies.

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

Historically, the principal source for treatment of congenital fibrinogen deficiency has been cryoprecipitate. Plasma-derived and viral-inactivated fibrinogen concentrates were shown by Dr. Arturo Pereira in 2007[4] to be safer and more specific in the treatment of congenital fibrinogen deficiency compared to cryoprecipitate.

1. Sorensen B and Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol 2010; 149: 834-43.
2. Rahe-Meyer N and Sorensen B. For: Fibrinogen concentrate for management of bleeding. J Thromb Haemost 2011; 9: 1-5.
3. Manco-Johnson MJ, Dimichele D, Castaman G, et al. Pharmacokinetics and safety of fibrinogen concentrate. J Thromb Haemost 2009; 7: 2064-9.
4. Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection. Haematologica 2007; 92: 846-9.

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

The FIBRYNA development program was conducted under IND 14777. A pre-BLA meeting was requested by the applicant on March 14, 2016 (CRMTS #10194) and a written response was issued to the applicant by the FDA on April 21, 2016 to answer the applicant's questions. There were no statistical questions raised in the meeting package or the response from the FDA.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission is adequately organized for conducting a complete statistical review of the primary efficacy endpoint without unreasonable difficulty.

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

5.1 Review Strategy

There are two clinical studies in this submission. One is a pharmacokinetic (PK) study, FORMA-01 and the other is a phase 3 study, FORMA-02. Study FORMA-02 was intended to be the primary source of evidence of safety and effectiveness study, and FORMA-01 is a supportive study for the MCF endpoint. Therefore, study FORMA-02 will be reviewed in detail and FORMA-01 will be briefly discussed.

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

The following documents and datasets for the BLA were reviewed. All data sources are included in the sponsor's eCTD submission located in the FDA/CBER Electronic Document Room (EDR).

BLA	125612/0	
	Module 1.14	Labeling
	Module 2.5	Clinical Overview
	Module 2.7	Clinical Summary
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.3.2	Study Reports FORMA-01: study report body
	Module 5.3.5.1	Study Reports FORMA-02: study report body, protocol, statistical analysis plan
	Module 5.3.5.1	Data Files FORMA-02: dm.xpt, zh.xpt, fa.xpt, lb.xpt, ex.xpt
	125612/0.23	
	Module 5.3.5.1	Study Reports FORMA-02: addendum to the clinical study report

5.3 Table of Studies/Clinical Trials

The following clinical studies, summarized in Table 1, are included in the submission.

Table 1 Summary of clinical studies in the BLA

Study No. **Status**	**Population** **No. of Patients Planned/Enrolled** **Planned (Enrolled) Age**	**Design** **Study Site/ Location** **Study Period**	**Test Product(s)** **Dosage Regimen** **Duration of Treatment**	**Evaluation Criteria**	**Endpoints**
Pivotal Study					
FORMA-02 Ongoing	Patients with congenital fibrinogen deficiency N=24/N=13 (as of 04-Mar-2016) ≥12 years (≥18 in Russia) (13–53 years)	Prospective Open-label Uncontrolled Phase III Multicenter 14 centers included in interim report Start: 13-Oct-2015 End: Q3 2020	*FIBRYNA* Treatment of BEs: *Minor bleeding*: to a target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL; additional doses to be administered only if fibrinogen plasma level on subsequent days is <80 mg/dL *Major bleeding*: to a target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL; additional doses to be administered only if fibrinogen plasma level on subsequent days is <130 mg/dL Surgical prophylaxis: *Minor surgeries*: to a target fibrinogen plasma level of 100 mg/dL and an accepted lower limit of 80 mg/dL for loading dose; additional doses to be administered only if fibrinogen plasma level on subsequent days is <80 mg/dL *Major surgeries*: to a target fibrinogen plasma level of 150 mg/dL and an accepted lower limit of 130 mg/dL for loading dose; additional doses to be administered only if fibrinogen plasma level on subsequent days is <130 mg/dL	Efficacy Safety IVR	*Primary endpoint* • Efficacy in treating the first documented BE of each patient *Secondary endpoints* • Efficacy • MCF* • Hemostatic efficacy in all BEs • Surgical prophylaxis • Fibrinogen concentration • IVR • Safety and tolerability (AEs, vital signs, laboratory safety, immunogenicity)
Supportive Study					

FORMA-01 completed	Patients with congenital fibrinogen deficiency N=22 ≥12 years (12–53 years)	Multinational Multicenter Prospective Randomized Controlled Crossover Phase II Multi-center: 10 centers in India, Switzerland, Iran, UK, USA and Bulgaria Start: 04-Jun-2013 End: 19-Jan-2015	FIBRYNA and comparator Haemocomplettan® P/RiaSTAP™ Single administration of 70 mg/kg Duration: Two periods of 45 days each	PK Efficacy* Safety	*Primary* • PK: AUC (fibrinogen) vs Haemocomplettan® P/RiaSTAP™ • Efficacy: MCF at 1 h post-infusion vs Haemocomplettan® P/RiaSTAP™ *Secondary (PK)* • T1/2, Cmax, Cmaxnorm, Tmax, MRT, Vss and CL *Secondary (efficacy and safety)* • IVR • Safety (AEs, vital signs, laboratory safety)

* MCF was used a surrogate efficacy endpoint.
Source: Original BLA 125612.0; Module 5.2, Tabular Listing of all Clinical Studies.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 Study FORMA-02

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective of FORMA-02 is to demonstrate the efficacy of FIBRYNA for on-demand treatment of acute BEs (spontaneous or after trauma).

The secondary objectives are as follows,

- To demonstrate the efficacy of FIBRYNA in preventing bleeding during and after surgery.
- To assess the safety of FIBRYNA in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions.

6.1.2 Design Overview

This ongoing study is a multinational, multi-center, prospective, open-label, uncontrolled, phase III study to assess the efficacy and safety of FIBRYNA for on-demand treatment of acute bleeding and surgical prophylaxis in subjects with congenital fibrinogen deficiency. The study plans to enroll 24 subjects. This planned interim analysis was conducted after 10 subjects, two of whom are under the age of 18 years, had experienced at least one BE.

<u>On-demand Treatment of Acute Bleeding</u>
Subjects presenting to the study site for an acute BE are to undergo a 30-day treatment and assessment cycle as outlined below. Throughout the study, subjects may undergo more than one 30-day cycle for treatment for additional BEs as required until the close of the study. At the end of their study participation, subjects are asked to return for a final study completion visit.

After the pre-infusion assessments, subjects receive the first infusion of FIBRYNA for treatment of bleeding. Subjects with minor bleeding are observed for at least 3 days. Subjects with major bleeding are observed for at least 7 days. The definition of minor and major bleeding is as follows,

- *Minor bleeding* events are mild hemarthrosis or superficial muscle, soft tissue, and oral bleeding.
- *Major bleeding* events are symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, or pericardial bleeding, or intramuscular bleeding with compartment syndrome, or bleeding causing a decrease in hemoglobin level by 20 g/L (1.24 mmol/L) or more.

If the subject required multiple infusions, the actual treatment duration was determined by the investigator based on his/her judgment of the subject's condition. On subsequent study days (at least 3 days for minor bleeding or 7 days for major bleeding), fibrinogen plasma levels are measured daily to determine whether additional infusions of FIBRYNA are needed. After these subsequent study days, dosing occurs as required depending on the actual and target plasma level.

Surgical Prophylaxis

Subjects undergoing elective surgery are also enrolled in the study. Within 3 hours prior to surgery, each subject receives a loading infusion of FIBRYNA to achieve a recommended fibrinogen plasma level of 100 mg/dL for minor surgeries and 150 mg/dL for major surgeries. Surgeries are defined as major, if any of the following criteria are met:

- Requiring general or spinal anesthesia.
- Requiring opening into the great body cavities.
- In the course of which hazards of severe hemorrhage is possible.
- Requiring hemostatic therapy for at least 6 days.
- Orthopedic interventions involving joints (ankle, knee, hip, wrist, elbow, shoulder).
- 3rd molar extraction or extraction of > 3 teeth.
- Surgeries/conditions in which the subject's life is at stake.

All other surgeries are classified as minor. The classification is made prospectively.

On each post-operative day, fibrinogen plasma levels were measured daily (at least 3 days for minor surgery and 7 days for major surgery) to determine whether additional infusions of FIBRYNA are needed. The surgical observation period was from Day 1 (i.e., the day of surgery) to the Last Post-Operative Day. The Last Post-Operative Day is either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever comes last. At the end of the study duration, all subjects were asked to return for a Study Completion Visit.

6.1.3 Population

Subjects who meet all of the following criteria were eligible for the study:

1. Aged ≥12 years.
2. Documented diagnosis of congenital fibrinogen deficiency, expected to require on-demand treatment for bleeding or surgical prophylaxis:
    a. Fibrinogen deficiency manifested as afibrinogenaemia or severe hypofibrinogenaemia.

b. Historical plasma fibrinogen activity of<50 mg/dL or levels below the limit of detection of the local assay method.

3. Having an acute bleeding episode (spontaneous or after trauma) or planning to undergo elective surgery.
4. Informed consent signed by the subject or legal guardian.

6.1.4 Study Treatments or Agents Mandated by the Protocol

FIBRYNA is individually dosed to achieve a recommended target fibrinogen plasma level dependent on the bleeding type (minor or major) or type of surgery (minor or major).

The target fibrinogen plasma levels were defined as follows:
Minor bleeding/minor surgery: 100 mg/dL and an accepted lower limit of 80 mg/dL.
Major bleeding/major surgery: 150 mg/dL and an accepted lower limit of 130 mg/dL.

If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, FIBRYNA should not be administered on that day.

6.1.6 Sites and Centers

Approximately 15 study centers worldwide were planned to enroll subjects and 14 centers were included in this IA. Three subjects are from India, and two subjects each are from the UK and Iran. The sites in the USA, Bulgaria, Turkey, Saudi Arabia, Lebanon, and Russia each enrolled one subject.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint
The primary endpoint is the overall clinical assessment of the hemostatic efficacy of FIBRYNA in treating the first documented BE of each subject. The first BE covers the time period from the first FIBRYNA infusion until 24 hours (i.e., 1 day) after the last infusion.

Each BE was assessed by the investigator and the IDMEAC. The overall clinical assessment of hemostatic efficacy for bleeding is based on a 4-point hemostatic efficacy scale as described in Table 2. The final efficacy assessment of each subject for the primary endpoint analysis was adjudicated by the IDMEAC. Ratings of excellent or good are considered successes.

Table 2 4-Point Hemostatic Efficacy Scale

Category	Definition
Excellent	Immediate and complete cessation of bleeding in the absence of other hemostatic intervention as clinically assessed by the treating physician; and/or <10% drop in hemoglobin compared to pre-infusion.
Good	Eventual complete cessation of bleeding in the absence of other hemostatic intervention as clinically assessed by the treating physician; and/or <20% drop in hemoglobin compared to pre-infusion
Moderate	Incomplete cessation of bleeding and additional hemostatic intervention required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in hemoglobin compared to pre- infusion.
None	No cessation of bleeding and alternative hemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in hemoglobin compared to pre-infusion.

Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 7.

The success criterion was pre-specified in the protocol as the lower limit of the two-sided 90% CI greater than 70% for the proportion of subjects with successful hemostatic efficacy rating.

Secondary Endpoints

The following secondary endpoints were included in this study.

- Efficacy of FIBRYNA in all BEs collected in the study using the investigator's overall clinical assessment of hemostatic efficacy for bleeding based on a 4-point hemostatic efficacy scale.
- MCF assessment before first infusion and 1 hour after end of first and last infusion of each documented BE.
- Efficacy of FIBRYNA in surgical prophylaxis was assessed at the end of surgery by the surgeon and post-operatively by the hematologist using the following scales:

Category	Definition
Intra-operative efficacy as assessed by surgeon (at the end of the surgery=after last suture)	
Excellent	Intra-operative blood loss* was lower than or equal to the average expected blood loss for the type of procedure performed in a subject with normal hemostasis and of the same sex, age, and stature.
Good	Intra-operative blood loss* was higher than average expected blood loss but lower or equal to the maximal expected blood loss for the type of procedure in a subject with normal hemostasis.
Moderate	Intra-operative blood loss* was higher than maximal expected blood loss for the type of procedure performed in a subject with normal hemostasis, but hemostasis was controlled.
None	Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.
*All excludes unexpected blood loss due to surgical complications, i.e., – Direct injury of a vessel (artery or vein) – Vessel injury not adequately responding to routine surgical procedures achieving hemostasis – Accidental injury of parenchymatous tissue (e.g., liver, lung)	
Post-operative efficacy as assessed by hematologist	
Excellent	No post-operative bleeding or oozing that was not due to complications of surgery. All post-operative bleeding (due to complications of surgery) was controlled with FIBRYNA as anticipated for the type of procedure.
Good	No post-operative bleeding or oozing that was not due to complications of surgery. Control of post-operative bleeding due to complications of surgery required increased dosing with FIBRYNA or additional infusions, not originally anticipated for the type of procedure.
Moderate	Some post-operative bleeding and oozing that was not due to complications of surgery; control of post-operative bleeding required increased dosing with FIBRYNA or additional infusions, not originally anticipated for the type of procedure.
None	Extensive uncontrolled post-operative bleeding and oozing. Control of postoperative bleeding required use of an alternate fibrinogen concentrate.

Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 8 and 9.

The IDMEAC conducts an independent adjudication of all hemostatic efficacy results and adjudicates the investigator's assessments of the intra- and post-operative assessments. The efficacy endpoint was derived from the adjudicated intra- and post-operative assessments according to the agreed algorithm presented in Table 3. In the event of an assessment falling into one of the categories marked 'Primary adjudication', the classification of success or failure was determined by the IDMEAC.

Table 3 Algorithm for the Adjudicated Intra- and Post-operative Assessments of Hemostatic Efficacy

Intra-operative assessment	**Post-operative assessment**			
	Excellent	**Good**	**Moderate**	**None**
Excellent	Success	Success	Success	Primary adjudication
Good	Success	Success	Primary adjudication	Failure
Moderate	Success	Primary adjudication	Failure	Failure
None	Primary adjudication	Failure	Failure	Failure

Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 10.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size

The planned sample size, 24 subjects, is limited by the very small number of subjects with this indication. Therefore, no sample size estimation was provided. At least 4 subjects are to be between 12 and 18 years old.

A sample of at least 4 surgeries is planned, 2 of which should be performed in subjects aged between 12 and 18 years.

Analysis Populations

Safety Population (SAFETY):

The safety population includes all subjects who received at least one infusion of FIBRYNA. The analysis of safety is based on this population.

Full Analysis Set (FAS):

The FAS is defined according to the intention-to-treat (ITT) principle and includes subjects who fulfil all of the following conditions:

- Received at least one infusion of FIBRYNA.
- Entered the study with a confirmed congenital fibrinogen deficiency.
- Presented with an episode of acute bleeding.
- And/or plan to undergo a surgical procedure with a need for at least one infusion of FIBRYNA during the time period from the day of surgery until overall clinical assessment of hemostatic efficacy.

Reviewer Comment:

This FAS definition is for both acute bleeding and surgery treatment. It will be described as FAS-Bleeding and FAS-Surgery in the rest of this memo.

Per-Protocol Population (PP):

The per-protocol (PP) population includes all subjects in the FAS who did not have any major protocol deviations.

The efficacy analyses were performed for BEs using the FAS and the PP population (PP analysis). Additional analyses were also performed for the surgical population.

Primary Efficacy Endpoint Analysis
The following hypotheses were tested on a (pre-specified) 5% one-sided level:

Null hypothesis H_0: $p \leq 0.7$
Alternative hypothesis H_A: $p > 0.7$

p = the proportion of subjects with successful hemostatic efficacy.

The point estimate and two-sided 90% CI from Blyth-Still-Casella were planned to be calculated.

Secondary Efficacy Endpoints Analysis
Efficacy of FIBRYNA in all Bleeding Episodes
The efficacy of FIBRYNA in the treatment of all BEs recorded throughout the study observation period was planned to be assessed in the same way as the efficacy of FIBRYNA in the treatment of the first BE per subject (please refer to the Primary Efficacy Endpoint Analysis above).

Surgical Prophylaxis
The efficacy of FIBRYNA in surgical prophylaxis was planned to be evaluated by descriptive statistics based on an overall assessment.

Missing data
In general, missing data was not planned to be imputed. If the hemostatic efficacy assessment is missing, it will be set to 'none' in the ITT analysis. Subjects with missing hemostatic efficacy assessment will be excluded from the PP population. Missing MCF values were not planned to be replaced.

Interim Analysis
An IA was planned to be performed after data was available for the first BE in 10 subjects; 2 of these subjects should be between 12 and 18 years old.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 4 shows the number of subjects were enrolled or analyzed for this IA report on March 25, 2016.

Table 4 Number of Subjects Enrolled/Analyzed

Population	Number of Subjects
Screened	23
SAFETY	13
FAS-Bleeding	11
PP-Bleeding	9
FAS-Surgery	4
PP-Surgery	4

6.1.10.1.1 Demographics

All 13 subjects were older than 12 years of age, with a median age of 30 years. Two subjects were between 12 and 18 years old. Of the 13 subjects, 9 were classified as White, 3 were classified as Asian and 1 as Arab/Middle-Easterner. The other baseline characteristics and demographics of the SAFETY population are shown in Table 5 and Table 6, respectively.

Table 5 Baseline Characteristics, SAFETY Population (N=13)

Parameter	Mean ± SD	Median (range)
Age (years)	30.7±13.0	30.0 (13-53)
Height (cm)	164.8±12.2	167.0 (149-190)
Weight (kg)	70.88±16.82	72.0 (34-99)
BMI (kg/m^2)	26.01±5.57	25.82 (14.34-39.64)

BMI = body mass index; SD = standard deviation.
Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 11.

Table 6 Demographics, SAFETY Population (N=13)

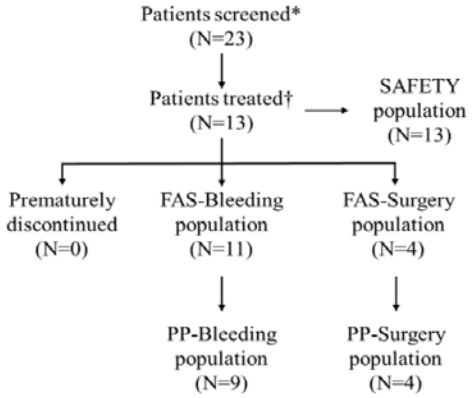
Parameter	N	%
Gender		
Male	7	53.8
Female	6	46.2
Race		
White	9	69.2
Asian	3	23.1
Other*	1	7.7
Congenital fibrinogen deficiency		
Afibrinogenaemia	13	100
Hypofibrinogenaemia	0	0

*Other = Arab/Middle-Easterner.
Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 11.

6.1.10.1.3 Subject Disposition

A summary of subject disposition is presented in Figure 1.

Figure 1 Subject Disposition



* "Patients screened" were screened and gave consent.
† "Patients treated" received FIBRYNA for the treatment of BEs or surgical prophylaxis are included in this interim analysis.
FAS = full analysis set; N = number of patients; PP = per-protocol.
Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Figure 1.

Two subjects ((b) (6)) were included in both the FAS-Bleeding and FAS-Surgery populations as they received treatment for both bleeding and surgical procedures. All subjects in the FAS-Bleeding and FAS-Surgery populations who up to the time of this IA had complete hemostatic efficacy data and received ≥90% of the planned total dose of FIBRYNA in the first infusion for bleeding or surgery were included in the PP-Bleeding or PP-Surgery population, respectively. Two subjects who received low FIBRYNA amounts on their first infusion for bleeding were excluded from the PP-Bleeding population. Thus, there are 9 subjects in the PP-Bleeding population. No subjects were excluded from the PP-Surgery population, so the final number of subjects in PP-Surgery population is 4.

Reviewer Comment:
One generalizability concern is worth raising here. There were no hypofibrinogenemia subjects in this study, which probably does not impact the efficacy but could have safety generalizability issues.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

Table 7 shows the results of the primary efficacy analyses. All of the first BEs was minor. Nine (81.8%) of the 11 first BEs were spontaneous and 2 (18.2%) were due to trauma. Hemostatic efficacy of 9 of these 11 BEs were rated as excellent and 2 were good by the investigator. Per the IDMEAC rating, the hemostatic efficacy of all 11 BEs was assessed as excellent. The rate of success for the treatment (efficacy rating of excellent or good) of the first BEs in each subject was 100% (11/11) and the 90% CI was 80% to 100% according to the investigator and the IDMEAC.

Table 7 Efficacy Assessment for Treatment of the First BE According to Investigator and IDMEAC

Efficacy Rating	**Investigator**		**IDMEAC**	
4-Point Scale	**N (%)**		**N (%)**	
Excellent	9 (81.8)		11 (100)	
Good	2 (18.2)		-	
Moderate	-		-	
None	-		-	
Missing	-		-	
Treatment Success*	**N (%)**	**90% CI**	**N (%)**	**90% CI**
Success	11 (100)	(80, 100)	11 (100)	(80, 100)
Failure				

* Efficacy rating of excellent or good indicated success and efficacy rating of moderate or none indicated failure.
Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 12.

Reviewer Comment:
(1) As the lower bound of the CI for the rate of successfully treated BEs was greater than 70%, the on-demand treatment results meet the pre-specified success criterion for this group of BEs.
(2) One subject, (b) (6) *, was identified by the clinical reviewer to be excluded from the final analysis. This subject was under-dosed by ½ the dose and did not experience an increase in fibrinogen level at 1 and 3 hours post dose, but both the investigator and IDMEAC rated the hemostatic efficacy as excellent. Since it is questionable whether the*

hemostasis efficacy was attributable to the product, a sensitivity analysis removed this subject from the FAS dataset. The success rate remains unchanged at 100% (10/10), but the lower bound of the CI decreases to 77.76%, and the pre-specified success criterion is still met.
(3) Of concern in this efficacy analysis is the generalizability of the results. Because all of the first BEs was minor, we do not have efficacy evidence for major bleeding episodes for this indication.

6.1.11.2 Analyses of Secondary Endpoints

Efficacy in the Treatment of all BEs:

The 11 subjects experienced a total of 23 BEs. All of the BEs are minor. Sixteen BEs (69.6%) were spontaneous and 7 (30.4%) were traumatic. A large majority of BEs (21/23) required only one FIBRYNA infusion (91.3%) and 2 (8.7%) BEs required two infusions (these were the first BEs in 2 subjects). The median (range) FIBRYNA dose administered for the treatment of all BEs was 57.5 mg/kg (33.9-71.4 mg/kg) per infusion and 58.8 mg/kg (33.9-101.7 mg/kg) per BE.

Of the 23 BEs, hemostatic efficacy was rated excellent for 19 BEs (82.6%) and good for 3 BEs (13.0%) by the investigator (one rating missing, considered a failure). Therefore, the success rate was 95.7% (22 of 23 BEs) and the 90% CI was 81% to 100%. The IDMEAC efficacy rating for all 23 BEs was excellent yielding a 100% success rate (90% CI: 88, 100).

Reviewer Comment:
Please refer to Reviewer Comment #2 in Section 6.1.11.1 regarding exclusion of subject (b) (6) *from the FAS dataset. Per this revised dataset, the success rate decreases to 95.45% (21/22) and the 90% CI is 80.44% to 99.52%.*

Efficacy in Surgical Prophylaxis:

Four subjects underwent four surgeries. Three surgeries were minor and one was major (right eye enucleation with socket reconstruction). A loading dose prior to surgery was administered for three surgical procedures. Median (range) loading FIBRYNA dose administered for all surgeries was 70.0 mg/kg (65.8-102.6 mg/kg). The mean (±SD) dose was 79.5 mg/kg (±20.1) per infusion. One minor surgery required two and the major surgery required seven post-operative infusions as per fibrinogen activity recommendations in the protocol. Median (range) FIBRYNA dose administered post-operatively was 20.5 mg/kg (12.8-34.1 mg/kg). The mean (±SD) dose was 20.8 mg/kg (±7.9) per infusion.

The intra-operative efficacy of FIBRYNA was rated as excellent in 3 (75%) minor surgeries and as good in 1 (25%) major surgery by the surgeon and the IDMEAC. The intra-operative success rate was 100% (90% CI: 50, 100).

The post-operative efficacy was rated as excellent in all four (100%) surgeries by the hematologist and as excellent in three (75%) surgeries (all minor) and good in one (25%) surgery (major) by the IDMEAC. The post-operative success rate was 100% (90% CI: 50, 100).

6.1.11.3 Subpopulation Analyses

Since the success rate for the primary efficacy endpoint was 100%, no differences were observed for any age, race and sex subgroup.

6.1.11.4 Dropouts and/or Discontinuations

There were no missing data for the primary, secondary and surgical endpoints.

6.1.12 Safety Analyses

6.1.12.3 Deaths

Up to the time of this IA, no deaths occurred in the study.

6.1.12.4 Nonfatal Serious Adverse Events

Two AEs in one subject were rated as serious and severe. The detailed information on the two SAEs is shown in Table 8.

Table 8 Listing of SAEs

Subject ID	MedDRA preferred term	Reason for seriousness	Outcome	Causality
(b) (6)	Ligament rupture	Hospitalization	Recovered with sequelae	Not related
	Patella fracture	Hospitalization	Recovered with sequelae	Not related

Source: Original BLA 125612.0; Module 5.3.5.1, Clinical Study Report, Table 27.

6.1.12.5 Adverse Events of Special Interest (AESI)

Two subjects were found to have anti-fibrinogen antibodies after protocol-defined testing at study start and neither subjects reported inhibitory effects in the past nor were any observed in this study. No subjects developed anti-fibrinogen antibodies during the study.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

There is no major statistical issue in this BLA submission. The submission includes the IA of an ongoing study, FORMA-02, a prospective, open-label, uncontrolled, phase 3 study. The primary efficacy endpoint is the proportion of subjects with a treatment success (hemostatic efficacy rating of excellent or good) for treated first BEs. The proportion of treatment success for the first BEs was 100% (11/11) and the 90% CI was 80% to 100%. The results achieve the pre-specified success criteria since the lower limit of the 90% CI exceeds 70%.

One subject, (b) (6) , was identified by the clinical reviewer to be excluded from the final analysis. This subject was under-dosed by ½ the dose and did not experience an increase in fibrinogen level at 1 and 3 hours post dose, but both the investigator and IDMEAC rated the hemostatic efficacy as excellent. Since it is questionable whether the hemostasis efficacy was attributable to the product, a sensitivity analysis removed this subject from the FAS dataset. The success rate remains unchanged at 100% (10/10), but the lower bound of the CI decreases to 77.76%, and the pre-specified success criterion is still met.

Four surgical procedures in four subjects for surgical prophylaxis were assessed and three procedures were classified as minor and one was classified as major. All four surgeries were rated as excellent or good by the IDMEAC, so the overall success rate was 100%.

The safety evaluation revealed that no subject reported inhibitory (anti-fibrinogen antibodies) effects in this IA for FORMA-02.

One concern is not related to statistical issues but it is worth mentioning here. My general reservation for the application is generalizability. There were no hypofibrinogenemia subjects were enrolled in FORMA-02, which probably doesn’t impact efficacy but could have safety generalizability issues. Meanwhile, there were only minor bleeds among the first BEs, so we do not have substantial efficacy evidence for major bleedings of this indication.

10.2 Conclusions and Recommendations

In this BLA submission, the primary efficacy endpoint of the pivotal study was the proportion of subjects with treatment success, where the hemostatic efficacy assessments were made for the treated first BEs. The results indicated that the lower bound of the 90% CI was higher than the pre-specified criterion. No safety concerns were noted. Therefore, the statistical evidence supports the proposed indication.

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IMPORTANT - DO NOT CHANGE ANYTHING BELOW THIS SECTION!
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