BLA Clinical Review Memorandum

Application Type	Efficacy Supplement
STN	125612/67
CBER Received Date	June 26, 2020
PDUFA Goal Date	Dec 24, 2020
Division / Office	DCEPT/OTAT
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Xiaofei Wang Karl Kasamon
Review Completion Date / Stamped Date	December 23rd 2020
Supervisory Concurrence	Bindu George Tejashri Purohit-Sheth
Applicant	Octapharma Pharmazeutika Produktionsges.m.b.H.
Established Name	Fibrinogen (Human)
(Proposed) Trade Name	FIBRYGA®
Pharmacologic Class	Freeze-dried human fibrinogen
Formulation(s), including Adjuvants, etc.	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized powder in single-use Bottles containing 1g fibrinogen to be reconstituted with 50mL Water for injection
Dosing Regimen	Based on target plasma fibrinogen level: Adult Dose (mg/kg) = [target level(mg/dL)-measured level (mg/dL)]/1.8 (mg/dL/mg/kg) Pediatric Dose (mg/kg) = [target level(mg/dL)- measured level (mg/dL)]/1.4 (mg/dL/mg/kg) If baseline level unknown: 70mg/kg
Indication(s) and Intended Population(s)	FIBRYGA is a human fibrinogen concentrate indicated for the treatment of acute bleeding episodes in adults, adolescents and children with congenital fibrinogen deficiency, including afibrinogenemia and

	hypofibrinogenemia. FIBRYGA is not indicated for dysfibrinogenemia.
Orphan Designated (Yes/No)	No

TABLE OF CONTENTS

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
IMP	Investigational Medicinal Product
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
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PP	per protocol
ROTEM	rotational thromboelastometry
TEAE	treatment emergent adverse event
WFI	water for injection

1. Executive Summary

This submission is an efficacy supplement for FIBRYGA (formerly referred to as OCTAFIBRIN and FIBRYNA), a plasma-derived fibrinogen concentrate licensed June 2017 for on-demand treatment of acute bleeding episodes (BE) in adults and adolescents (≥12 years old) with congenital fibrinogen deficiency (CFD). The applicant has submitted clinical data to support treatment of bleeding events and perioperative management of pediatric subjects <12 years of age conducted under the study, FORMA

04. Approval of a treatment of bleeding in pediatric subjects <12 years of age is intended to fulfill the Pediatric Research Equity Act (PREA) Postmarketing requirements (PMR), which enrolled pediatric subjects with congenital fibrinogen deficiency age <12 years, assessed safety and efficacy for acute bleeding and included pharmacokinetics (PK) evaluation. The Applicant also provided data to support perioperative management of adults and adolescent subjects evaluated under the FORMA 02 study and additional efficacy data for treatment of bleeding in adults and adolescents an indication that was approved in 2017. However, this additional efficacy data particularly for one major bleeding event in adults and adolescents in the FORMA 02 study is considered supportive in evaluating the efficacy of treatment of bleeding in pediatric subjects < 12 years of age.

The indication for (b) (4) triggered a priority review as there are no US FDA approved products for this indication.

FORMA 02 and FORMA 04 are similar in design in that subjects with BEs are infused to post-infusion target plasma fibrinogen level of 100 mg/dl for minor BEs (lower limit of target range 80 mg/dl) and a level of 150 mg/dl for major BEs (130 mg/dl lower limit of target range). Efficacy was assessed in both studies using the same four-point hemostatic efficacy scale based on criteria such as bleeding cessation, changes in hemoglobin, and use of any other hemostatic assessments, graded by the investigator and adjudicated by IDMEAC. Both studies observed subjects with minor BEs for ≥ 3 days, and subjects with major BEs for ≥ 7 days, additional infusions of FIBRYGA were administered on subsequent days if fibrinogen levels decreased to < the lower limit of the target range during this period. Success was defined as hemostatic efficacy score of excellent or good, whereas moderate or none indicated failure. FORMA 04 in addition included a single dose pharmacokinetic (PK) portion with 14-day monitoring of study drug levels.

With respect to perioperative management, FORMA 02 and FORMA 04 were similar in design with subjects infused to achieve a target plasma fibrinogen level of 150 mg/dl for major surgery (lower limit of target level 130 mg/dl), and a level of 100 mg/dl for minor surgery (lower limit of target level of 80 mg/dl). The surgeon graded the intraoperative hemostasis on a four-point efficacy scale at completion of surgery, followed by a daily wound-healing score, and these outcomes were adjudicated by IDMEAC. Subjects undergoing minor surgeries were observed for ≥ 3 days, and subjects with major surgeries for ≥ 7 days. Additional infusions of FIBRYGA were administered on subsequent days if fibrinogen levels decreased to < the lower limit of the target range during this period. Success was defined as hemostatic efficacy score of excellent or good, whereas moderate or none indicated failure.

Pharmacokinetics
Pharmacokinetic parameters, including incremental *in vivo* recovery (IVR), were assessed following infusion of FIBRYGA in 13 subjects under 12 years of age in Study FORMA 04. Among the 8 subjects aged 6 to < 12 years old, the median incremental IVR was 1.4 mg/dL/mg/kg (range 1.27-2.10), whereas among 5 subjects <6 years of age, the median incremental IVR was 1.3 mg/dL/mg/kg (range 1.28-1.44). These findings are in contrast to an incremental IVR of 1.8 mg/dL (range 1.08-2.62) determined in earlier studies and have significant implications for dosing. When a patient's fibrinogen level is known, dosing of FIBRYGA is based on a formula which incorporates this IVR value, thus allowing age-appropriate dosing.

Treatment of Bleeding Events
In FORMA 04, eight subjects experienced a total of 10 bleeds, of which 2 were major and 8 were minor. Both subjects who had major BEs did not successfully achieve target mean fibrinogen levels. The subjects with minor bleeding achieved the target levels, although there were discrepancies in the actual vs. protocol specified dose. Treatment of the 10 bleeds were rated as excellent or good by reviewer adjudication.

Sub-target fibrinogen levels and delayed success with hemostasis in the 2 major bleeding events were observed. However, these are likely attributed to the pharmacokinetic findings, and dosing recommendations will take the PK findings into account for pediatric dosing in children < 12 years of age.

Perioperative Management of Bleeding
In FORMA 02, perioperative hemostatic efficacy was assessed in 9 subjects treated with FIBRYGA for 12 surgeries, of which one was major and 11 were minor. The subject who underwent major surgery had a hemostatic efficacy score of good. Overall efficacy was rated as successful in all surgeries; however, there were dosing discrepancies and irregularities, which included infusion of substantially higher doses than specified per protocol in several subjects. In the case of one subject, the post infusion preoperative fibrinogen level failed to rise adequately even after a second infusion, and one subject did not receive an infusion on the day of surgery because of a measurable fibrinogen level from treatment of a BE a couple days earlier.

In FORMA 04, hemostatic efficacy was assessed in three subjects treated for the perioperative management of one major (splenectomy) and two minor surgeries (tooth extraction, circumcision) and achieved a 100% success rate in the age 0 to <12-year-old group. However, there were no surgical data in subjects aged 6 to <12 years. The subject who underwent major surgery did not reach target fibrinogen levels following the presurgical infusion, and there were several dosing discrepancies involving multiple subjects infused with substantially higher doses of FIBRYGA than specified by the protocol. Safety assessment of the 25 subjects treated with FIBRYGA revealed 91 adverse events among 19 subjects. Three were classified as possibly related to FIBRYGA. Of 15 serious AEs, one was graded as possibly related to treatment (thrombosis).

Conclusion:
Efficacy of FIBRYGA for treatment of acute bleeding: the benefit/risk profile is favorable for the treatment of acute bleeding in children < 12 years of age. The dosing recommendations have been revised in the label to specify an incremental in vivo recovery (IVR) of 1.4 mg/dl/mg/kg for patients < 12 years of age in comparison to the recommended IVR of 1.8 mg/dl/mg/kg for adolescents and adults.

(b) (4)

(b) (4)

Safety of FIBRYGA appears similar in children aged <12 to adolescents and adults, but thrombosis remains a concern and warrants the ongoing adult/adolescent safety PMR study to further evaluate this, to which children under 12 should be incorporated.

Regulatory recommendation:
The risk-benefit considerations support granting an indication for the treatment of bleeding episodes in children <12 years of age with appropriate revisions for dosing in children. This study fulfills the PREA PMR requirement for this indication. (b) (4)

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The FORMA 02 Full analysis set (FAS) for the BEs population (N=25) was comprised of the following groups:

- 18 (75%) White, 5 (21%) Asian, 1 (4.2%) Other (Arab)
- 1 was Hispanic/Latino
- 6 were 12 to <18 years of age
- 13 (54%) males
- 11 (46%) females

The FORMA 02 perioperative management population (N=9) was comprised of the following groups:

- 7 (77.8%) male
- 2 (22.2%) female
- 5 (55.6%) White, 3 (33.3%) Asian 1 (11.1%) Other (Arab)
- 1 (11.1%) was < 18 years of age

The FORMA 04: Full Analysis Set for the BEs population was comprised of (N=14) subjects <12 years old.
Among the FAS population:

- 6 (42.9%) <6 years old
- 8 (57.1%) 6 to <12 years old
- 10 (71.4%) White
- 4 (28.6%) Asian
- 8 (57.1%) female
- 6 (42.8%) male

The studies were international due to the rarity of fibrinogen deficiency, and demographics were relatively representative of the Asian and Middle- Eastern

countries which enrolled many of the subjects, with a relative underrepresentation of African American, Latino or Far-East Asian groups.

1.2 Patient Experience Data

Clinician reported outcomes, comprised of hemostatic efficacy ratings for the treatment of bleeding events and intraoperative and post-operative bleeds, were vital endpoints in this study and are provided in this submission. Patient reported outcomes (PROs) were not part of the evaluation of the product in this study nor were they provided in the submission.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	Not applicable.
☐	Observer-reported outcome	Not applicable
☒	Clinician-reported outcome	Sec 6.1 Study endpoints. Tables 3,4,5.
☐	Performance outcome	Not applicable
☐	Patient-focused drug development meeting summary	Not applicable
☐	FDA Patient Listening Session	Not applicable
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	Not applicable
☐	Observational survey studies	Not applicable
☐	Natural history studies	Not applicable
☐	Patient preference studies	Not applicable
☐	Other: (please specify)	Not applicable
☒	**If no patient experience data were submitted by Applicant, indicate here.**	Not submitted
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	Not applicable
☐	Patient-focused drug development meeting	Not applicable
☐	FDA Patient Listening Session	Not applicable
☐	Other stakeholder meeting summary report	Not applicable
☐	Observational survey studies	Not applicable
☐	Other: (please specify)	Not applicable

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

The management of Congenital fibrinogen deficiency (CFD) has not changed appreciably in terms of available therapy since licensing of FIBRGYA for on demand treatment of BEs in June of 2017.

Fibrinogen is a glycoprotein encoded by three different genes and is the major structural component of clot. It has a fair long half-life of 3-4 days, and plasma concentrations in humans average 200-400 mg/dl. CFD is a rare disorder, prevalence approaching 1:1,000,000, with autosomal recessive inheritance. Several mutations have been identified. Bleeding occurs in 80% of patients with afibrinogenemia, about 10% is intra-cranial hemorrhage (ICH). Neonatal presentation with umbilical stump bleeding is a frequent presenting sign, bleeding can affect the skin and the genitourinary, gastrointestinal, and nervous systems. Frequency of bleeding events is variable, but patients have approximately 0.5-0.7 bleeding episodes annually, Bleeding risk and severity is likely to increase as the fibrinogen level decreases below 100 mg/dL. Patients with congenital fibrinogen deficiency generally require on-demand treatment of acute bleeding and peri- operative management with fibrinogen replacement therapy (FRT). Prophylaxis is occasionally used during pregnancy (to prevent miscarriage or post-partum hemorrhage) and following a life-threatening bleeding event such ICH. FRT is based on achieving target levels of fibrinogen. FRT is the mainstay of treatment of acute bleeding events, perioperative management. FRT and dosing of fibrinogen is primarily based on the Guidelines issued in 2004 by the United Kingdom Haemophilia Center Doctors' Organization. Afibrinogenemia and hypofibrinogenemia are linked to paradoxical thrombosis.

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

Current therapy consists of replacement therapy for bleeding episodes (BE). Available FRT options include fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, and the licensed fibrinogen (from pooled human plasma) RiaSTAP (CSL Behring), all targeted to achieve a plasma concentration fibrinogen of 100 mg/dL.

2.3 Safety and Efficacy of Pharmacologically Related Products

Please see prior review (2017) for full discussion of this section, as no new agents have been approved in the U.S. since that time.

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

FIBRYGA has been approved in 23 countries: Austria, Belarus, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, Germany, Hungary, Luxembourg, Poland, Portugal, Singapore, Slovakia, Slovenia, Sweden, Switzerland, United Kingdom, the United States of America and Uruguay

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

Correspondence History (obtained from the original review memo 2017):

- IND submission of the FORMA 02 study on December 14, 2011.
- IND submission of a revised protocol for FORMA 02 study under Amendment 3 on January 30, 2013, relate to:
    - Revisions to the surgical protocol
    - Exclusion of subjects with dysfibrinogenemia and pregnant women within 20 weeks of gestation
    - Inclusion of subjects 12-17 years of age
    - Proposal for a formal hypothesis testing based on successful hemostatic efficacy of >70%
- On November 23, 2013, FDA reviewed the revised Phase 3 FORMA 02 study submitted under Amendment 8 of IND 14777 and provided the following comments to the following revisions:
    - The primary efficacy endpoint was to be based on assessment of hemostatic efficacy for the first bleeding episode. Assessment of hemostatic efficacy for the subsequent bleeding episodes was a secondary endpoint. FDA requested justification for evaluating only the first bleeding episode for the primary efficacy analysis. FDA requested that the Independent Endpoint Adjudication Committee (IDEAC) rather than the Independent Data Monitoring Committee (IDMC) adjudicate the final efficacy assessment for each subject.
    - An objective measure for restoration of hemostasis was requested.
- Advice/Information Request dated 14 Apr 2016:
  Refer to 28 Sep 2015 submission to IND application for Octafibrin (FIBRYGA was previously referred to as Octafibrin) and the FDA had the following comments and requests for further information: (Question 2). “FDA suggest increasing the number of subjects to enroll six for each group (treatment and perioperative) to assess PK data as six total subjects may not give an accurate representation of this assessment.”

  Within the response from Octapharma was the following: “The FORMA-04 study was not part of the pre-IND meeting discussion with the FDA. The paediatric committee (PC) of the EMA has reviewed the criteria to be applied to data submitted to support approval for the indication of fibrinogen replacement in this population and, because of the rarity of the disorder, has agreed to the patient numbers included in this protocol for post approval

submission. In fact, it will be very difficult to recruit and enroll even this modest number of patients within a reasonable time frame (our current estimate of the time required to complete enrollment is 5 years). We appreciate the motivation for the suggestion to increase the number of patients; however, we believe the proposed number of patients, as deemed by the PC as meeting the pediatric requirements for the EMA, is a reasonable approach to balancing the goals of obtaining clinically useful PK data and completing patient enrollment in an acceptable time frame."

- Pre-BLA meeting (CRMTS#10194), April 22, 2016
  - Octapharma inquired if the proposed clinical package would suffice for the indication "Treatment of acute bleeding episodes (b) (4) in adult and pediatric subjects with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia". FDA responded that determination for licensure will be made upon review of the data provided with the BLA.
  - In an advice letter sent under IND 14777 on April 15, 2016, FDA requested that the Applicant include in the BLA submission additional analyses, analyzing data by sex (appreciating the small number of subjects) and assessment of AEs by the applicant in addition to the assessment of AEs by the investigators.
  - FIBRYGA was approved by the agency on June 9, 2017 for the indications of acute bleeding episodes and adult and adolescent subjects with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.
  - In an advice letter sent under IND 14777 on July 10 2017, FDA noted to Octapharma that the statistical considerations section of the study protocol noted that hemostatic efficacy would be based on the totality of data for bleeding episodes (b) (4) , but the hypothesis testing did not include a testing approach for (b) (4) . Applicant was urged to submit a new protocol or revision and seek agreement thereof, if they were planning to seek future marketing approval for the (b) (4) indication.

June 26, 2020, DCC receipt date of the following:

- Applicant submitted final study report for PMC #1 as noted in the approval letter for STN 125612/0 dated June 7, 2017
- Included the <12 years of age group children for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency
- Included the indication for (b) (4) (i.e. Congenital Fibrinogen Deficiency)

- Proposed updates to and rewording of the product's the prescribing information label based upon FORMA 02 and FORMA 04, both completed since original BLA.

2.6 Other Relevant Background Information

Not applicable

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 practices, including informed consent, site-specific requirements, and in accordance with acceptable ethical standards. BIMO inspections were conducted for data from study FORMA-02 in 2017 before the product, Fibryga, was licensed in April 2017 and the inspections did not note significant deficiencies. Given the current global public health emergency and the geographic location of the study sites, the BIMO Branch recommended a waiver of BIMO inspections in support of this submission and the Review Committee concurred with this recommendation. Please see BIMO memorandum for full details.

Applicant-identified protocol deviations in FORMA 02. No subject was discontinued from either study due to a protocol violation. Two subjects in FORMA 02 were excluded from per-protocol populations in the BE treatment portion of the study and were analyzed and reviewed during the application process in 2017.

3.3 Financial Disclosures

Covered clinical study (name and/or number): FORMA 04
Was a list of clinical investigators provided? x Yes ☐ No (Request list from applicant)
Total number of investigators identified: 5
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

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: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): _____

Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

.

Covered clinical study: FORMA 02

Was a list of clinical investigators provided? x Yes ☐ No (Request list from applicant)

Total number of investigators identified: 12

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

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: _____

Significant payments of other sorts: _____

Proprietary interest in the product tested held by investigator: _____

Significant equity interest held by investigator in sponsor of covered study: _____

Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)

Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☐ No (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3): _____ Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant)

No significant concerns were raised following review of financial disclosures.

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

4.1 Chemistry, Manufacturing, and Controls

There are no updates to the CMC information in this supplement. Please refer to original BLA review memo from 2017 for CMC relevant information.

4.2 Assay Validation

Please refer to original BLA CMC review memo from 2017.

4.3 Nonclinical Pharmacology/Toxicology

There is no new Pharmacology/Toxicology (PT) information in this submission. Please refer to the original PT review memo from 2017.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

FIBRYGA provides replacement for fibrinogen, a critical soluble plasma protein in the coagulation cascade.

4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of FIBRYGA are the same as those of endogenous fibrinogen. Refer to the 2017 original Clinical Pharmacology review for additional details.

4.4.3 Human Pharmacokinetics (PK)

FORMA 04 contained a single dose PK evaluation in subjects under 12 years old. Please see pharmacology review memo for more details. Briefly, compared to adults and adolescent subjects, children < 12 years old had lower incremental in vivo recovery (IVR), shorter half-life and faster clearance. The median IVR were 1.32 mg/dL/mg/kg and 1.42 mg/dL/mg/kg for children < 6 years and ≥6 to <12 years group, respectively, compared to an IVR of 1.77mg/dL/mg/kg noted in adolescent and adult subjects in FORMA 01. The dosing recommendations for treatment of acute bleeding episodes in children less than 12 years of age will include an IVR of 1.4 mg/dL/mg/kg in the dosing formula.

4.5 Statistical

The applicant's calculations were reproducible, and no statistical concerns were identified. Statistical reviewer has corroborated and evaluated the Applicant's statistical findings, please refer to the statistical review memo for additional details.

4.6 Pharmacovigilance

As part of the routine pharmacovigilance surveillance, MedDRA queries are used to review cases from the Drug Safety Database to identify potential risks as well as missing information. Pharmacovigilance review did not identify any new safety signals.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

This efficacy supplement review focused on data from Study FORMA 04, to evaluate FIBRYGA for the indication of on demand bleeding treatment in pediatric subjects with CFD. Analyses were performed largely using JMP 14 (SAS Institute, Inc.) based on the submitted data analysis datasets.

For the perioperative management in subjects with CFD, data from the perioperative section of Study FORMA 02 were reviewed, as these data related to subjects aged 12 and above. Data from FORMA 04 related to perioperative management in pediatric subjects <12 years of age was reviewed for this age group. Safety data from FORMA 02 and FORMA 04 were also reviewed. Bleeding treatment efficacy data in adults and adolescents from FORMA 02 were previously reviewed by the agency for licensing of FIBRYGA and will not be re-evaluated herein.

For the following reasons, the subsections listed below were omitted from this review:

- Previously submitted with BLA 125612/0
    - 3.2 Compliance with Good Clinical Practices and Submission Integrity
- No new data included in this submission
- 4.1 Chemistry, Manufacturing, and Controls
- 4.3 Nonclinical Pharmacology/Toxicology
- Irrelevant to this submission
    - 2.6 Other Relevant Background Information
    - 4.2 Assay Validation
    - 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound
    - 8.5.9 Person-to-Person Transmission, Shedding

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

Modules 1 and 5 were the primary sources of information for the clinical review, including draft labeling, study reports, and datasets, from study FORMA 04 and the perioperative and safety portions of FORMA 02.

5.3 Table of Studies/Clinical Trials

Table 1 Clinical studies of FIBRYGA

Protocol	Type	Phase	Design	N Subjects	Prime Endpoint
FORMA 02	Pivotal, efficacy, Safety	3	Multinational, Prospective, Open-label, Uncontrolled	N=24 Full Analysis set for first BEs. Six age 12 to 17 years. Eighteen > 17 years old.	Hemostatic efficacy in on demand treatment of BEs

FORMA 04	efficacy, Safety, PK	3	Multinational, Prospective, Open-label, Uncontrolled	N = 8 BE N =13 PK All <12 years old	Hemostatic efficacy in on demand treatment of BEs

(Source: Adapted from 5.2 Tabular Listing of All Clinical Studies, page 2-5.)

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The BLA was not referred to an Advisory Committee because the review of information submitted in the BLA, including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefitted from an advisory committee discussion

5.4.2 External Consults/Collaborations

External consultations were not requested as additional scientific expertise was not necessary to complete the review of this supplement.

5.5 Literature Reviewed (if applicable)

Tziomalos K, Vakalopoulou S, Perifanis V, Garipidou V. Treatment of congenital fibrinogen deficiency: overview and recent findings. Vasc Health Risk Manag. 2009;5:843-848. doi:10.2147/vhrm.s5305

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

FORMA 04
Prospective, open-label, uncontrolled, phase III study to assess the efficacy, safety, and pharmacokinetics of FIBRYGA for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency.

6.1.1 Objectives (Primary, Secondary, etc.)

Primary:
To demonstrate the efficacy of FIBRYGA for on-demand treatment of acute bleeding episodes (BEs) (spontaneous or after trauma).

Secondary:

- To determine the single-dose pharmacokinetics (PK) of FIBRYGA in pediatric subjects with congenital fibrinogen deficiency.
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1-hour post-infusion
- To determine the response to FIBRYGA based on incremental in vivo recovery (IVR)
- To demonstrate the efficacy of FIBRYGA in preventing bleeding during and after surgery

- To assess the safety of FIBRYGA in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions

6.1.2 Design Overview

Prospective, open-label, uncontrolled, phase III study to assess the efficacy, safety, and pharmacokinetics of FIBRYGA for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in pediatric subjects with congenital fibrinogen deficiency.

Reviewer's Comment: FORMA 04 was similar in design to the adult/adolescent trial that preceded it, FORMA 02. Due to rarity of CFD, no control arm was included in the study. The study has the expected limitations of being a small, uncontrolled, unblinded study. Although study success criteria were not pre-specified, descriptive statistics coupled with supportive data in the adult and adolescent data and achievement of target fibrinogen levels were considered in the assessment of efficacy in pediatric subjects <12 years of age.

6.1.3 Population

FORMA 04 mirrored inclusion and exclusion criteria of FORMA 04, except criteria applicable to the pediatric study population, given that all FORMA 04 subjects were under 12 years of age. For example, the pediatric study did not specifically exclude subjects abusing illicit drugs, or breast feeding.

6.1.4 Study Treatments or Agents Mandated by the Protocol

FIBRYGA is a human plasma-derived fibrinogen concentrate for intravenous use. The product is packed and labelled according to local regulations in vials containing 1 g of lyophilized fibrinogen concentrate powder for reconstitution with 50 mL of water for injection (WFI). It was administered as an intravenous bolus injection at a maximum speed of 5 mL/min. Continuous infusion was not allowed. Three batches of Octafibrin (previous name for FIBRYGA) were used throughout the study. The batch numbers were A441A3471, A441A3472 and K619A3493.

Reviewer comment: Octafibrin was the name applied to the investigational product at the time the studies were launched, later changed to FIBRYNA, and shortly after licensing, to the current name, FIRBYGA.

6.1.5 Directions for Use

Each vial of FIBRYGA will be reconstituted with 50 mL sterile water for injection (WFI). The solvent (i.e., WFI) and the concentrate in the closed vials must be warmed up to room temperature. Room temperature must be maintained during reconstitution. FIBRYGA dissolves at room temperature to an almost colorless and slightly opalescent solution within 30 minutes. If the solution is cloudy or contains particulates, it should not be used. The solution should not be frozen. FIBRYGA should be administered immediately after reconstitution at a rate not exceeding 5 mL per minute. FIBRYGA should not be mixed with other medicinal products or intravenous solutions. FIBRYGA will be administered as intravenous (i.v.) bolus injection not exceeding an injection rate of 5 mL per minute.

6.1.6 Sites and Centers

- Sahyadri Specialty Hospital, Pune, India.
- St. John's Medical College Hospital, Bangalore, India.
- S.S Institute of Medical Science and Research Center, Davangere, India.
- Hotel De Dieu de France, Beirut, Lebanon.
- Nemazee Hospital Shiraz University of Medical Sciences, Shiraz, Islamic Republic of Iran

6.1.7 Surveillance/Monitoring

For on demand treatment of BEs, each bleeding event started a monitoring period that lasted 30 days. Each subject was observed for a minimum of 3 days in the case of minor and 7 days in the case of major BEs. Similarly, surgical subjects were observed for 3 or 7 days following each minor, and major surgery, respectively. Detailed flow charts of the monitoring regimen are included in Appendix, FORMA 04 section.

.

No specific concerns were identified by the Applicant with respect to monitoring the conduct of the clinical investigations.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the clinical assessment of each subject's first BE. A secondary efficacy endpoint was the clinical assessment of all BEs occurring during the study observation period, using the same 4-point scale. The approach used to determine efficacy scores is outlined in Table 3.

Table 2 Clinical Assessment of hemostatic Efficacy for Treatment of Bleeding.

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: CSR page 26)

Secondary Endpoints:

Incremental In Vivo Recovery (IVR)

Response IVR was calculated as the maximum increase in plasma fibrinogen (i.e., (b) (4) data) between the pre-infusion and the 3-hour post-infusion measurement (expressed as absolute concentration in plasma [mg/dL]), divided by the exact dose of FIBRYGA (expressed as mg/kg dosed).

Classical In Vivo Recovery
Classical IVR was calculated as the maximum increase in plasma fibrinogen (i.e., (b) (4) data) between the pre-infusion and the 3-hour post-infusion measurement (expressed as absolute concentration in plasma [mg/dL]), divided by the total dose of FIBRYGA per expected plasma volume (expressed as mg/dL). The expected plasma volume was estimated based on the blood volume formula described by Nadler et al.

Perioperative management Perioperative management
Efficacy outcomes were assessed by the surgeon using 4-point hemostasis scale on completion of case (Table 4), and by hematologist using a post-operative scale (Table 5). These outcomes were adjudicated by the IDMEAC, who also considered the surgeon's review of the case. Adjudication by IDMEAC followed schema in Table 6.

Table 3 Surgeon's hemostatic assessment at end of surgery

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 exclude 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)

(Source: CSR Page 27)

Table 4 Hematologist's post-surgical hemostasis assessements

o 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 FIBRYGA 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 FIBRYGA 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 FIBRYGA or additional infusions, not originally anticipated for the type of procedure.
None	Extensive uncontrolled post-operative bleeding and oozing. Control of post- operative bleeding required use of an alternate fibrinogen concentrate.

(Source: CSR Page 27)

Adjudication algorithm for hemostatic efficacy for perioperative management of bleeding

Table 5

Intra-operative assessme	**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: CSR Page 28)

Reviewer's comment:

Hypofibrinogenemia leads to a variety of bleeding manifestations throughout the body, and the severity of these events spans a continuum from mild to life threatening. Devising metrics to quantify cessation of such a gamut of bleeding presentations to implement in a clinical study, is very challenging. Consequently, several of the subjects' outcomes needed information requests (IRs) sent to allow review of clinical data necessary for the reviewer to adjudicate outcome, especially if disparity between score from investigator vs. IDMEAC was noted, or their scores appeared to be unfounded. Unfortunately, for several subjects there was no data available for periods of time while on treatment, precluding or at least complicating assessing hemostasis.

The study endpoints aim to detect and quantify the clinical benefit of providing fibrinogen activity to subjects with CFD who present with an active bleed. Endpoints rely on clinical assessment by the investigator, which consider achievement of hemostasis, improvement in pain, swelling, bruising or function, and also integrate blood loss, which would be expected to be clinically significant mainly with severe BEs and major surgery. A limitation is the subjective nature of the investigator's evaluation, and the difficulty in ascribing pain reduction to treatment effect rather than decreased inflammation following traumatic injury. The endpoints were appropriate and similar to those used in the earlier

adult/adolescent study, and a four-point scale of hemostatic efficacy has been used for regulatory review of efficacy assessment in products used to treat coagulation disorders.

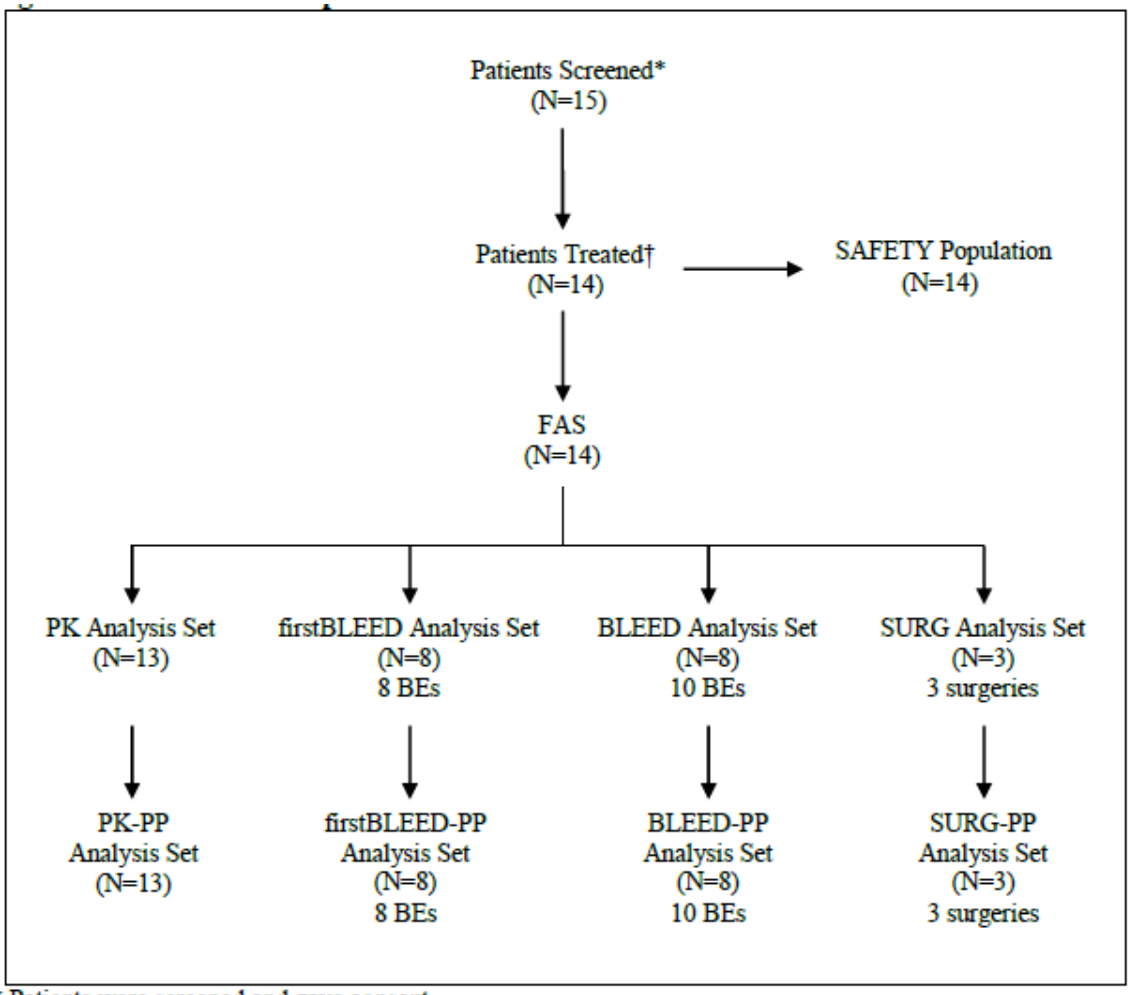
6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary endpoint is the overall clinical assessment of the hemostatic efficacy of FIBRYGA in treating the first documented bleeding episode in each subject. The first bleeding episode covers the time period from the first Octafibrin infusion for the treatment of a bleeding episode until 24 hours (i.e., 1 day) after the last infusion or the end of the treatment observation period, whichever comes last. For the analysis, the assessment made by the investigator on the 4-point rating scale was transformed to a dichotomous endpoint with success defined as a rating of excellent or good. The final efficacy assessment of each patient was adjudicated by an IDMEAC. The bleeding efficacy data were summarized using descriptive statistics and displayed graphically, differentiating between the first bleeding episode per patient (primary endpoint) and all bleeding episodes (secondary endpoint).

6.1.10 Study Population and Disposition

Disposition of subjects enrolled, treated and analyzed in FORMA 04 is presented in Figure 1.

Figure 1. Subject Disposition



* Patients were screened and gave consent.
† Patients received *Octafibrin* for PK analysis, treatment of a BE or surgical prophylaxis.
BE = bleeding episode; FAS = full analysis set; N = number of patients; PP = per-protocol; PK = pharmacokinetic

Figure 1 Subject disposition (Source: CSR page 44)

6.1.10.1 Populations Enrolled/Analyzed

For the analysis of this study, the following populations were to be considered:

- SAFETY population: Subjects who fulfilled all the inclusion criteria and met none of the exclusion criteria for the study, and who received at least one infusion of FIBRYGA.
- Full analysis set (FAS): the FAS was defined according to the intention-to-treat (ITT) principle included subjects in the study who fulfilled all of the following conditions:
    - Received at least one infusion of the IMP
    - Entered the study with a confirmed congenital fibrinogen deficiency
- Pharmacokinetic (PK) analysis set: all subjects in the FAS who started the PK assessment and had at least one valid post-baseline fibrinogen activity level.

- Bleeding analysis set (BLEED): all documented BEs treated with FIBRYGA in the FAS population
- Surgical analysis set (SURG): all FAS subjects with documented surgical interventions with at least one infusion of the IMP during the time period from the day of surgery until day of overall clinical assessment of post-operative efficacy

6.1.10.1.1 Demographics

FORMA 04 was a multinational, multicenter study due to rarity of the disease studied. Table 7 summarizes these data.

Table 6 FORMA 04 Demographics

Sex	**Number (%)**
Female	8 (57.1)
Male	6 (42.9)
Age	
<6 year	6 (42.9)
6 to <12	8 (57.1)
Race	
White	10 (71.4
Asian	4 (28.6)
Ethnicity	
Non-Hispanic/Latino	14 (100)
Hispanic/Latino	0 (0)

(Source: Adapted from FORMA 04 CSR Page 47)

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

All subjects had congenital afibrinogenemia or hypofibrinogenemia. Other coagulopathies were specifically excluded.

6.1.10.1.3 Subject Disposition

For the safety analysis population, no material deviations were noted. All of the subjects who received the infusions are included in the safety analysis. One subject who was in the BE analysis and perioperative management analysis discontinued the study prematurely due to the development of a portal vein thrombosis. Refer to Figure 1. above.

6.1.11 Efficacy Analyses

Hemostatic activity of FIBRYGA assessed for the subjects' first BE was the planned primary efficacy endpoint. The rationale for these criteria in the primary efficacy analysis was to minimize the theoretical undue influence on overall results from a few subjects with multiple BE. Hemostatic efficacy for all BEs was considered as a secondary endpoint. However, because FORMA 04 included eight first BEs and only two second BEs (none beyond second), and the two second BEs had typical outcomes, we analyzed efficacy in all BEs, rather than 1st BEs in analysis, given the rarity of the disease and small number of events.

6.1.11.1 Analyses of Primary Endpoint(s)

Overall, hemostatic efficacy was documented excellent or good (successful) for the treatment of all eight first BEs (100%) according to the IDMEAC compared to six first BEs (75%) according to the investigator. As noted earlier, this review will focus primarily on the evaluation of efficacy in all BEs rather than first BEs. Please refer to Analyses of Secondary Endpoints.

6.1.11.2 Analyses of Secondary Endpoints

Efficacy of FIBRYGA in treatment of all BEs was evaluated as the efficacy endpoint. Eight subjects in FORMA 04 were treated for a total of 10 BEs. Of these, 5 (50%) BEs were spontaneous and 5 (50%) were due to trauma. Minor bleeding included oral, vaginal (first menarche), scrotal bleed, arm bleeds, and subcutaneous facial hematoma. Major bleeds were a knee and thigh traumatic hematomas, and an intraperitoneal bleed following a spontaneous spleen rupture. A total of 8 (80.0%) BEs were considered minor, with the remaining 2 BEs (20.0%) classed as major. All eight of the minor bleeds required only one infusion, compared to the major bleeds, where one subject received three infusions and one received four infusions. See Table 9 below.

Table 7 All BEs treatment outcomes and FIBRYGA doses.

Type of Bleeding Event/Target Fibrinogen Level 1 hr post infusion	Age Group	Outcomes all Bleeding Events (BEs) (n=10 total bleeds including major & minor)	Mean Fibrinogen Level post 1 hr after infusion (mg/dl)	Mean Dose FIBRYGA (mg/kg)
Major Bleeding (Fibrinogen target 150mg/dl. minimal limit 130mg/dl)	0-6 yrs (n=1)	Excellent (n=0) Good (n=1)	110	75
	>6-12 yrs (n=1)	Excellent (n=0) Good (n=1)	118	79
Minor Bleeding (Fibrinogen target 100mg/dl. minimal limit 80mg/dl)	0-6 yrs (n=3)	Excellent (n=3) Good (n=1)	96.5	77.7
	>6-12 yrs (n=3)	Excellent (n=4) Good (n=0)	96.2	49.7

(source: Reviewer's calculations from data from FORMA 04 module 16 Appendices, datasets lb.xpt, and zh.xpt)

For the following three BEs, scores ascribed by IDMEAC and by this reviewer were not in agreement:

Subject (b) (6) had intraperitoneal hemorrhage from spontaneous splenic rupture and was infused for this BE on Day 1, which elevated his fibrinogen level to 110 by 1h post infusion. Although it was reported that he was not retreated on Day 2 because of improved hemostasis, he received additional infusions of FIBRYGA on Days 3, 5 and 9 (4 doses total). Due to his surgery (splenectomy), no hematologic efficacy assessment was performed by the investigator at 24h after last infusion for grading hemostatic efficacy of the BE.

The subject's hemoglobin dropped by 32.6% between Baseline and Day 2. IR response from the Applicant explained that the subject's hemoglobin drop was possibly related to fluid resuscitation and fluid shifts, and that gradually his hemoglobin level rose spontaneously to ~ 8.5g/dL, consistent with a net hemoglobin drop of 10-15%. However, given lack of definitive documentation of hemostasis by clinical means, and the drop in hemoglobin, this reviewer accepts an abdominal ultrasound from Day 6 as unequivocal evidence that hemostasis was achieved at some point before Day 6. Day 6 would not constitute immediate hemostasis, but eventual, hence our adjudicated score of *good*.

This subject did not reach target fibrinogen levels on the first nor subsequent days until Day 5, when his 1h post infusion level was 153 mg/dl.

Subject (b) (6) had a major BE of traumatic thigh hematoma. She was infused on Day 1 and had additional infusions on Days 2 and 3, but no description of her clinical response was available. She achieved 1-h post infusion fibrinogen levels of 118, 131, and 135 mg/dl on Days 1, 2, and 3, respectively. Only the Day 3 level met the lower end of the target dose, but the preceding levels were measurably over 100 mg/dl, and thus likely to have therapeutic effect. The investigator scored her hemostatic efficacy as moderate, the IDMEAC adjudicated it as excellent, but given no clinical evidence of hemostasis until Day 4, this reviewer adjudicated her outcome as *good* (consistent with eventual, but not immediate hemostasis).

Subject (b) (6) had a minor BE of traumatic oral hemorrhage, and while the investigator graded her efficacy as excellent, it was documented that by Day 4, her hemoglobin dropped by 17%. There was no adequate explanation of the hemoglobin drop in the setting of this BE, hence, by protocol definition, this reviewer adjudicated her hemostatic efficacy as *good*.

In summary, as adjudicated by this reviewer, 3 of the 10 BEs were graded as good hemostatic efficacy, and 7 as excellent, and thus 100% (95% CI 69.15–100.00) of the BEs were rated as successful with respect to hemostatic efficacy.

Dosing discrepancies:
Among the subjects treated for minor BEs, the protocol dose targeted a fibrinogen level of 100 mg/dl using a formula which took into account the difference between the target fibrinogen level and the baseline fibrinogen level of the subject. This difference is then divided by the incremental IVR of 1.8 mg/kg. The IVR was a factor determined in an older PK study (FORMA 01). Several subjects treated for minor BEs were dosed with a substantially higher dose of FIBRYGA than calculated by the protocol dose and the formula guiding clinician use in the product label, see Table 8.

Table 8 FORMA 04 dosing discrepancy, and dose using proposed peds IVR of 1.4

ID	Baseline fibrinogen (mg/dl)	Target level (mg/dl)	1h post inf. Fibrinogen (mg/dl)	Investigator dose administered FIBRYGA (mg/kg)	Reviewer FIBRYGA dose (per protocol) (mg/kg)	FIBRYGA dose calculated by applicant (mg/kg)	Age-adjust (peds) 1.4 IVR Dose (mg/kg)
(b) (6)	10	150*	118	79.1	77.8	79.11	100
	0	100	79	**70**	**55.5**	56	71
	0	100	108	**63.83**	**55.6**	56.49	71
	0	150*	110	75	83.3	86.75	107
	0	100	106	**93.75**	**55.6**	56.5	71
±	0	100	107	**78.95**	**55.6**	56.47	71
	0	100	94	68.57	55.6	56.49	71
	20	100	86	45.19	44.4	45.19	57
±	20	100	83	45.21	44.4	45.21	57
	20	100	90	45.18	44.4	45.21	57

±Second BE for subject. *Target dose 150 for major BE.

(Source: Adapted from CSR section 16.2.5 Compliance and/or Drug Concentration Data). Numbers in **bold** point out dose discrepancies.

Reviewer's comment: Hemostatic efficacy was rated as successful in all BEs treated. The discrepancies seen in a number of subjects where actual doses given tend to be substantially higher than if correctly dosed per protocol (and if one were to follow current FIBRYGA package insert (PI) recommendations, are of concern. It is unknown if the subjects' hemostasis success rates would have been as good if lower FIBRYGA doses were administered as per the protocol formula. However, looking at the 1 h post infusion fibrinogen level achieved by the investigator's given dose in column 4 is reassuring in that none of the subjects achieved a dangerously high (with respect to potential thrombotic risk) fibrinogen level, nor even substantially above target (maximal 108 mg/dl, with target of 100 mg/dl in Subject (b) (6)). However, the fibrinogen levels in for the treatment of major BEs failed to reach target levels despite the supra-protocol doses given. It is possible that the PK studies failed to adequately predict the necessary dose to treat major BEs, because they are determined in a static situation without ongoing blood loss and consumption. Nevertheless, age-specific IVR dosing should improve outcomes, and based on PK results, the IVR for pediatric subjects < 12 years of age is recommended to be 1.4 mg/dL/mg/kg.

Efficacy in Perioperative management

Three subjects received FIBRYGA for perioperative management for a total of three surgeries. Of these, two surgeries were minor (circumcision and tooth pulpectomy) and one was major (splenectomy). Although the loading dose of FIBRYGA was sufficient to treat minor surgeries, the loading dose to treat the major surgery in one subject was inadequate and the subject required five post-surgical infusions.

Actual blood loss did not exceed maximum expected blood loss for any procedure. No intra-operative transfusions were administered and none of the 3 surgeries resulted in postoperative bleeding.

The subject who underwent major surgery was infused FIBRYGA preoperatively which raised the fibrinogen level to 120 mg/dl intraoperatively; However, his postoperative fibrinogen level decreased to 57 mg/dl. He was given additional infusions on Days 3, 6, 8 10, and 13. The 1-h post infusion level remained below the 150 mg/dl target level and was noted to be130 mg/dl (lower limit of target level) until postop Day 12. As for the treatment of BEs, all subjects treated perioperatively also tended to have substantially higher doses of FIBRYGA administered than per protocol the formula. See Table 10.

Table 9 FORMA 04 Perioperative Management target fibrinogen levels & FIBRYGA doses

Subject ID	Baseline fibrinogen (mg/dl)	Target level (mg/dl)	Investigator dose administered FIBRYGA (mg/kg)	Reviewer FIBRYGA dose (per formula) (mg/kg)	FIBRYGA dose calculated by applicant (mg/kg)
(b) (6)	0	100	**71.43**	**55.6**	56.5
(b) (6)	87*	150	**50**	**35**	35.6
(b) (6)	0	100	**102.94**	**55.6**	84.76

*Target dose 150 for major surgery (splenectomy). The baseline value of 87mg/dl is residual from dose given previously for BE. (Source: Adapted from CSR section 16.2.5 Compliance and/or Drug Concentration Data).

(b) (4)

[redacted]

Pharmacokinetics:
Please see pharmacology review memo for further details, briefly:

- Compared to adults and adolescent, children < 12 years had lower incremental IVR, shorter half-life and faster clearance.
- Median IVR was 1.32 mg/dL/(mg/kg) and 1.42 mg/dL/(mg/kg) for children < 6 years and 6 to <12 years, respectively.
- (The IVR for adults in current product labeling is 1.8.)
- Based on available IVR information from FORMA 04, FIBRYGA dose should be optimized for pediatric patients by modifying the dosing formula, to use the age-specific IVR of 1.4 for all subjects less than 12 years of age.

Reviewer's comment:
The PK portion of this study suggests that due to shorter half-life and faster clearance of FIBRYGA in children than adolescents/adults, children should be dosed with a modification of the formula that takes into account their PK characteristics. Since the adult/adolescent formula relies on the median incremental IVR of 1.8 mg/dl/mg/kg, and FORMA 04 revealed that the median incremental IVR in children ages 0 to <12 is 1.4 mg/dl/mg/kg, pediatric subjects should be dose based on age-specific formula, adapted with the corresponding incremental IVR of 1.4 mg/dl/mg/kg. This correction for unique pediatric pharmacokinetics should help optimize the doses that children would receive.

6.1.11.3 Subpopulation Analyses

Due to small numbers, no subpopulations were analyzed.

6.1.11.4 Dropouts and/or Discontinuations

The subject with who developed the SAE of portal vein thrombosis was discontinued from study and started on anticoagulant therapy.

6.1.11.5 Exploratory and Post Hoc Analyses

None

6.1.12 Safety Analyses

6.1.12.1 Methods

Summary characteristics of FORMA 04 adverse effects (AEs):

The SAFETY population comprised of 14 subjects and was exposed to a total of 36 infusions of IMP. Four of these subjects (28.6%) experienced a total of 10 AEs. The data were catalogued using MedDRA version 18.1. AEs were categorized as mild, moderate or severe. There were no deaths. There was one non-fatal serious AE (portal vein thrombosis), which was considered possibly related to FIBRYGA, and this SAE led to premature discontinuation of the subject from study.

Safety was assessed in FORMA 04 by monitoring vital signs and physical examination of subjects, in addition to routine laboratory testing and collecting AE information at clinical follow up visits. AEs included treatment emergent adverse events (TEAEs), which were those occurring after the start of the first FIBRYGA infusion and before a 30-day observation period following each BE, or during the surgical observation period. Also, non-TEAEs, which were defined as AEs that occurred outside of the observation period.

Investigators evaluated subjects for anti-fibrinogen antibodies before the first exposure to FIBRYGA, and then on Day 30 after each BE treatment. Thrombogenic potential was evaluated by a measurement of plasma levels of prothrombin fragment (F1+F2) and D-dimer, before and after each FIBRYGA infusion for BE, except for the last day of infusion.

6.1.12.2 Overview of Adverse Events (AEs)

The total AEs are summarized in Table 11 below with respect to intensive, seriousness, resolution and relatedness to FIBRYGA.

Table 10

Adverse effects	**N**	**%**
Total Adverse Effects	10	100
Intensity		
MILD	7	70
MODERATE	2	20
SEVERE	1	10
Serious Event		
YES	1	10
NO	9	90
Resolved		
YES	9	90
NO	1	10
Related to FIBRYGA		
YES	0	0
NO	8	80
POSSIBLY	2	20

(Source: Reviewer's compilation of data from 125612 67 dataset ae.xpt)

All AEs resolved with the exception of the portal vein thrombosis which, did not resolve by the end of the subject's participation in the study following his discontinuation. Most common AEs by system organ class (SOC) included: skin and subcutaneous tissue disorders of ecchymosis in 2 subjects, and general disorders and administration site conditions of pyrexia and influenza-like illness, and tonsillitis in one subject each. Other less common AEs included musculoskeletal disorders such as ankle hemarthrosis, and hepatobiliary disorders (portal vein thrombosis) in one subject. Two AEs were possibly treatment related as judged by the investigator, portal vein thrombosis and pyrexia, in one subject.

6.1.12.3 Deaths

None

6.1.12.4 Nonfatal Serious Adverse Events

The only SAE in the study occurred in Subject (b) (6), who developed portal vein thrombosis following treatment of a BE for spontaneous spleen rupture and splenectomy. While there exists an association between spleen rupture and portal vein thrombosis, and even greater association between splenectomy and portal vein thrombosis, the applicant appropriately characterized this SAE as possibly related to treatment product.

Subject (b) (6) was hospitalized and treated for spontaneous spleen rupture that required several doses of FIBRYGA, and then underwent splenectomy on day 10 of hospitalization. Shortly before surgery, he was infused and was recorded as having no perioperative bleeding. On postoperative Day 1, the subject was not infused FIBRYGA. On postoperative Day 2, although the subject had no bleeding, he had a fibrinogen level <130 mg/dL, and therefore was prophylactically infused with FIBRYGA. On postoperative Days 3 and 4, he was reported to have no bleeds and no infusion given, although slight abdominal pain was reported. On postoperative 5, although no bleeds were reported, the subject was infused due to worsening abdominal pain. He was diagnosed with portal vein thrombosis noted on Doppler ultrasound and started on therapy for the thrombosis. On postoperative Day 6, he had no bleeds, and no infusion was given. On post-operative Day 7, no bleeds were reported, but he did have an infusion. On postoperative Day 9, no bleeds were reported, and no treatment was given. On postoperative Day 12, he received the last (sixth) infusion and no bleeding reported. The subject was discontinued from study. The investigator considered the SAE as not recovered and not resolved. No other subjects discontinued the study due to an adverse event.

Prothrombin F1+F2 and D-dimer levels in this subject were elevated before infusion of FIBRYGA for peritoneal hemorrhage due to spleen rupture and remained elevated following infusion with FIBRYGA. This subject also developed the laboratory abnormality of acute thrombocytosis, with platelet count reaching over 1000 x 10^9/L at the peak, which likely was related to splenic rupture (asplenia is a common cause of

thrombocytosis1), as an acute phase reaction due to his presenting splenic rupture. While such (likely reactive) thrombocytosis generally improves, often resolving by 30 days, no subsequent data regarding platelet counts is available in this case.

Reviewer's Comment:
The majority of AEs reported during FORMA 04 were mild or moderate, non-serious, temporary occurrences typical of the general population. Based upon the available data, these events do not represent a clinically significant safety concern. The severe AE of portal vein thrombosis was plausibly related to FIBRYGA. This is of particular concern, given the paradoxical propensity of patients with CFD toward thrombosis; however, in this case, splenic rupture and splenectomy occurred shortly before the SAE, and are also known to be associated with portal vein thrombosis. The subject was discontinued from the study and started on anticoagulant therapy. The pending FORMA 07 Postmarketing Requirement study in adults and adolescents, is in planning stages to further evaluate this signal further. Because the thrombotic risk in patients with CFD appears to affect all age groups, this reviewer recommends that subjects aged <12 years of age are added to this safety PMR study.

6.1.12.5 Adverse Events of Special Interest (AESI)

Thrombogenicity

Six subjects in FORMA04 were found to have abnormal prothrombin F1+F2 levels at baseline before infusion. Among 8 subjects whose prothrombin F1+F2 levels were normal at baseline, 2 developed a subsequent elevation above normal. Of subjects with normal D-dimer levels before infusion, 2 developed abnormal levels after infusion.

CFD carries paradoxical risk of thromboembolic complications. Portal vein thrombosis which occurred in a subject following splenectomy was plausibly related to FIBRYGA, although splenectomy is also a risk factor. The subject was discontinued from the study and started on anticoagulant therapy. The subject who suffered the portal vein thrombosis had elevated baseline levels of prothrombin F1+F2 and D dimer, and they remained abnormal throughout his study period.

Immunogenicity

The study employed an (b) (4) anti-fibrinogen antibody test to screen subjects and identified positive results in two subjects. One subject had these antibodies at baseline before infusion of FIBRYGA, and the other developed the antibody at Day 30 after treatment. However, neither manifested any clinical signs related to the antibodies and had successful BE treatments as graded by IDMEAC (Subjects (b) (6)).

Reviewer's comment:
FORMA 04 demonstrated a favorable safety profile of FIBRYGA therapy in subjects with congenital fibrinogen deficiency in children < 12 years of age. The rarity of the disease and small population sizes, especially in clinical situations with highest risk, requiring repeated administrations of FIBRYGA, major surgery and major bleeding events, limits this assessment. The two adverse events

1 Khan PN, Nair RJ, Olivares J, Tingle LE, Li Z. Postsplenectomy reactive thrombocytosis. *Proc (Bayl Univ Med Cent)*. 2009;22(1):9-12. doi:10.1080/08998280.2009.11928458

ascribed potentially to FIBRYGA, (pyrexia and portal vein thrombosis) might have been related to other causes, such as occult infection, and spleen rupture or splenectomy, respectively. However, given the known risk of paradoxical thrombosis in patients with hypofibrinogenemia, and the risk of thrombosis from published literature following fibrinogen replacement therapy, the thrombotic risks needs further evaluation in a post-marketing requirement (PMR), and supports modification of the current PMR study in adults/adolescents age 12 and above, to include pediatric subjects.

6.1.12.6 Clinical Test Results

Subject (b) (6), who underwent splenectomy for splenic rupture, developed thrombocytosis. This is likely multifactorial, related splenectomy and acute stress of the hemorrhage and surgery.

6.1.12.7 Dropouts and/or Discontinuations

Subject (b) (6) was diagnosed with an SAE of portal vein thrombosis on Postoperative Day 5 after his splenectomy (major surgery). Causality was categorized as possibly related to FIBRYGA, and this reviewer agrees with this assessment. He was started on anticoagulant therapy, and discontinued from study, but his SAE was considered unresolved by the end of study period. This serious thrombotic event is concerning and supports enrollment of pediatric subjects in the ongoing PMR safety study. Portal vein thrombosis is a known sequela of splenectomy, and even splenic rupture.

6.1.13 Study Summary and Conclusions

Pediatric subjects with CFD treated with on-demand FIBRYGA for BEs have demonstrated successful outcomes in several minor BEs and in the two major BEs. While there was a pattern of dosing discrepancies, and the major BE subject tended to achieve sub-target fibrinogen levels, the data support extending the indication of BE treatment to the pediatric age group taking into account dose modifications based on PK results. The PK portion of this study suggests that a modification of the formula for dosing FIBRYGA to optimize the formula to age category of 0 to <6 years old by use of an incremental IVR of 1.3 mg/dl/mg/kg, and to age category of 6 to <12 years old by utilizing an incremental IVR of 1.4 mg/dl/mg/kg, would likely give improved fibrinogen targets and hopefully translate to better outcomes, especially in major BEs.

(b) (4)

6.2 Trial #2

FORMA 02
Title: Prospective, open-label, uncontrolled, phase 3 study to assess the efficacy and safety of FIBRYGA for on-demand treatment of acute bleeding and perioperative management subjects with congenital fibrinogen deficiency.

6.2.1 Objectives (Primary, Secondary, etc)

Primary Objective:

To demonstrate the efficacy of FIBRYGA for on-demand treatment of acute BEs (spontaneous or after trauma).

Secondary Objectives:

- To demonstrate the efficacy of FIBRYGA in preventing bleeding during and after surgery.
- To achieve a peak target plasma fibrinogen level of 100 mg/dL in minor bleeds and 150 mg/dL for major bleeds 1-hour post-infusion.
- To assess the safety of FIBRYGA in subjects with congenital fibrinogen deficiency, including immunogenicity, thromboembolic complications, and early signs of allergic or hypersensitivity reactions.

6.2.2 Design Overview

This was an open-label, single-arm study, planned for a duration of 3 years. Individualized doses of FIBRYGA were given targeting a fibrinogen plasma level of 150 mg/dL for major bleeding or major surgery and 100 mg/mL for minor bleeding or surgery. Subjects were observed for ≥3 days if BE were minor or for ≥7 days if BEs were major and were to receive maintenance infusion if their fibrinogen levels were below the lower end of the target range (130 mg/dl for major BE, and 80 mg/dl for minor BE). After FIBRYGA administration, hemostatic response of BE was graded, as were intra and post-operative outcomes. Participants were observed for safety events up to 30 days following the first infusion.

Reviewer Comment: A target plasma fibrinogen level of 150 mg/dL for major surgery and BE management are higher than the level typically used in clinical practice for fibrinogen replacement therapy (FRT) of 100 mg/dL.

6.2.3 Population

Key inclusion criteria

- Age ≥12 years
- Documented diagnosis of congenital fibrinogen deficiency, expected to require on demand treatment for bleeding or perioperative management:
- Congenital afibrinogenemia or severe hypofibrinogenemia (plasma fibrinogen activity <50 mg/dL or antigen below limit of detection of the local assay
- Expected to have an acute BE (spontaneous or after trauma) or planning to undergo elective surgery.

Key exclusion criteria

- Bleeding disorder other than afibrinogenemia, including dysfibrinogenemia
- Treatment with any fibrinogen-containing product within 2 weeks
- Any coagulation-active drug within 1 week before start of treatment for BE or surgery or before 24 hours after the last FIBRYGA infusion.

- Hypersensitivity to study medication or plasma proteins
- Deep vein thrombosis or pulmonary embolus within 1 year
- Arterial thrombosis within 1 year
- Bleeding esophageal varices
- Liver disease (Child-Pugh B or C)
- Pregnancy within the first 2 weeks or currently breast-feeding
- Known HIV infection (viral load >200 particles/µL
- Multiple trauma within 1 year
- Diagnosed or suspicion of anti-fibrinogen inhibitor currently or in the past

Reviewer Comments: Certain categories of high thrombotic risk subjects were excluded from the study population therapy, reducing external validity of the safety data. Congenital fibrinogen deficiency (CFD) patients are known to carry increased risk of paradoxical thrombosis. Excluding them from a study where thrombosis might be provoked by FRT, limits the generalizability of the safety data. However, venous or arterial thrombosis history was not disqualifying, but had to have occurred over a year prior to study enrollment. Similarly, subjects with serious hemorrhagic complication history, like intracranial hemorrhage, were permitted. These features help make the studied population more reflective of the CFD population in general.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Table 12 summarizes the study treatments, dosing and follow-up periods.

Table 11. Target Fibrinogen Levels and Observation per Type and Serverity of BE and Surgery

Treatment Indication	Pre-infusion Target Plasma Fibrinogen level	Post-infusion acceptable lower limit of Plasma Fibrinogen*	Post-treatment follow-up	Comments
Minor Bleeding & Minor Surgery	100 mg/dL	80 mg/dL	Minimum of 3 days	FIBRYGA was administered 3 hours prior to surgery
Major Bleeding & Major Surgery	150 mg/dL	130 mg/dL	Minimum of 7 days.	FIBRYGA was administered 3 hours prior to surgery

*Maintenance infusions were administered if levels were lower than the acceptable post-infusion limits. Additional dose of FIBRYGA was not permitted if the plasma fibrinogen level was above or equal to the acceptable lower limit.

FIBRYGA dose was calculated individually based on the following formula:

$$\text{Fibrinogen dose (mg/kg body weight)} = \frac{\text{[Target peak plasma level (mg/dL) – measured level (mg/dL)**]}}{\text{Median response* (mg/dL per mg/kg body weight)}}$$

*The median response in this dose calculation formula is the median incremental in vivo recovery reported in the final analysis of study FORMA-01.
**The measured level for the first infusion will be the historical level for that patient after a washout or, if below the limit of detection of the local assay, zero (0) will be used.

Major bleeding was defined as symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, retroperitoneal, intraarticular or pericardial, intramuscular bleeding with compartment syndrome, or bleeding causing a decrease in hemoglobin by at least 2 g/dL. Minor bleeding was defined as mild hemarthrosis, superficial muscle and soft tissue and oral bleeding.

Major Surgery was defined as those surgeries for which the following criteria were met:

- Requiring general or spinal anesthesia
- Requiring opening into the great body cavities
- Severe hemorrhage was possible
- Requiring hemostatic therapy for at least 6 days
- Orthopedic interventions involving the hip, knee, ankle, wrist, elbow, shoulder.
- 3rd molar extraction or extraction of ≥ 3 teeth
- Life-threatening surgeries

Investigator discretion was allowed in classifying the type of surgery if not listed above.

Concomitant Medications

- Permitted Medications: Rescue therapy was permitted at the investigator's discretion and included the option of RiaSTAP.

Prohibited Medications: Non-steroidal anti-inflammatory drugs, warfarin, coumarin derivatives, platelet aggregation inhibitors were not permitted within 24 hours of FIBRYGA infusion, up to 1 week prior to surgery and treatment of bleeding episodes.

6.2.5 Directions for Use

The directions were the same as in FORMA 04. Four batches of FIBRYGA were used throughout study FORMA 02. The batch numbers were C343A3471, C343B3471, K616A3491 and K619A3494.

6.2.6 Sites and Centers

Multinational collection of centers including in: United States (1), United Kingdom (2), Bulgaria (1), Turkey (1), Saudi Arabia (1), Lebanon (1), Russia (1), India (3), Iran (2)

6.2.7 Surveillance/Monitoring

Please refer to charts detailing observation schema in the various portions of FORMA 02 in the Appendix under study FORMA 02.

6.2.8 Endpoints and Criteria for Study Success

Efficacy Endpoints:
Primary:

- Hemostatic efficacy: Success was based on the investigator's clinical assessment of hemostatic activity in treating the first documented BE for each subject using a four-point rating scale, as discussed in section 6.2.11. Success was defined as a rating of "excellent" or "good".

Key Clinical Secondary Endpoints:

- Fibrinogen plasma level before and 1 hour after the end of each subsequent
- as well as at the time of the overall clinical assessment of hemostatic
- efficacy (i.e. at 24 hours) after treatment of BE episode)
- Efficacy in all bleeding episodes using the overall clinical assessment of hemostatic efficacy based on a 4-point hemostatic efficacy scale
- Efficacy of FIBRYGA in preventing bleeding during and after surgery as assessed at the end of surgery by the surgeon and post-operatively by the hematologist using two 4-point hemostatic efficacy scales.

Key Safety Endpoints:

- Thrombogenic complications
- Allergic or hypersensitivity reactions following treatment administration
- Immunogenicity assessments as performed on days 14 and 30 days following the infusion of FIBRYGA

The safety observation period following treatment for acute bleeding was 30 days. For subjects being evaluated for perioperative management of bleeding, the safety observation period extended from the day of surgery to the last post-operative day which was anticipated to be three days for minor surgery and eight days for major surgery or the last day of infusion, whichever came last.

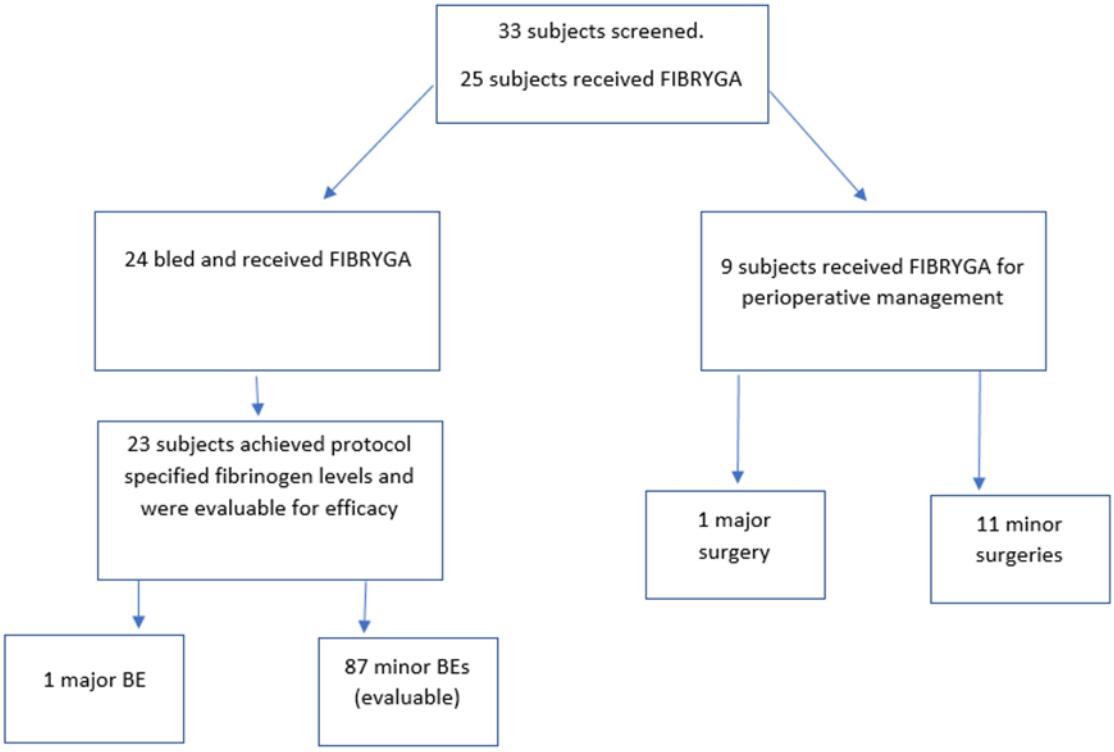
6.2.9 Statistical Considerations & Statistical Analysis Plan

Please see original review memorandum from 2017 for detailed presentation of statistical plan and the Statistical reviewer's review memo for this efficacy supplement.

6.2.10 Study Population and Disposition

Figure 2 below outlines the disposition of subjects in the arms that enrolled subjects for treatment of perioperative and acute bleeding episodes.

Figure 2. FORMA 02 Study Subject disposition



Safety population N=25. Full analysis set (FAS) N=24 for bleeding events. 89 BEs were treated, but two were excluded from analysis (unevaluable/protocol deviation). Perioperative management population N= 9, underwent 12 surgical procedures. (Source: CSR page 42)

6.2.10.1 Populations Enrolled/Analyzed

Safety population: All subjects who received at least one infusion of FIBRYGA.

Full analysis set (FAS) – defined according to intention to treat. All subjects who met all of the following criteria:

- Received at least one infusion of FIBRYGA.
- Entered the study with a confirmed congenital fibrinogen deficiency.
- Presented with an episode of acute bleeding or underwent a surgical procedure with a need for at least one infusion of FIBRYGA.

Two subpopulations: FAS-bleeding (treated for BE) and FAS-surgery

6.2.10.1.1 Demographics

Table 12 Demographic information FORMA 02

Parameter	**Subjects treated for BE (n= 24) (%)**	**Subjects treated for Surgery (N=9)**
Sex		
Male	13 (54.2.6)	7 (77.8)
Female	11 (45.8.3)	2 (22.2)

Race

White	18 (75)	5 (55.6)
Asian	5 (20.8)	3 (33.3)

Ethnicity

Other (Arab)	1(4.2)	1(11.1)
Hispanic/Latino	0 (0)	0(0)

Age

Age 12 to <18	6 (25)	1(11.1)
Age ≥18	18(75)	8(88.9)

Plasma fibrinogen levels that define afibrinogenemia and hypofibrinogenemia are variable, but in most cases levels of ≤ 10mg/dL has been used to define afibrinogenemia levels and fibrinogen levels ≥ 10 to ≤ 50mg/dL are used to define hypofibrinogenemia

All subjects met the enrollment criterion for fibrinogen deficiency based on the documented history of congenital fibrinogen deficiency and the demographics of the study population are consistent with the target patient population. (Source: Derived from Table 12 CSR Page 45.)

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
Three subjects had a prior history of intracerebral hemorrhage, one had a history of surgery for intracranial hemorrhage and one had portal vein thrombosis history. Splenectomy occurred in 5 subjects, one had a history of 5 miscarriages, one had thrombophlebitis, one had Budd Chiari, one had occult GI bleed, one had spontaneous sub-dural hematoma, and one had vasculitis.

Reviewer Comment: Inclusion of subject with hemorrhagic and thrombotic risks from prior events is representative of the CFD population. Prior history of intra cranial hemorrhage did not impact interpretability of the efficacy results.

6.2.10.1.3 Subject Disposition
A total of 33 subjects were enrolled. Eight of these did not experience any BEs or require any surgical procedures during the study period and were not infused with study drug, therefore they were not included in the analysis. The full analysis set (FAS) population was comprised of 25 subjects, of which 6 were between 12 and 17 years of age. At least one dose of FIBRYGA was infused for 89 BEs and 12 surgeries. No subjects dropped out of FORMA 02 due to AEs.

6.2.11 Efficacy Analyses

Although the protocol specified hemostatic efficacy of FIBRYGA for treatment of the first BE in each subject as the primary efficacy endpoint, given the rarity of the disease, we considered the hemostatic efficacy for all BEs as the primary endpoint. A four-point hemostatic efficacy scale was utilized to grade BE treatment outcomes, adjudicated by IDMEAC. See Table 14 for details.

Table 13 Four-Point scale for assessment of hemostatic efficacy for BEs, surgery, and postoperative bleeding.

Category	Bleeding Event	Intraoperative	Post-operative
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.	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.	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 *FIBRYGA* as anticipated for the type of procedure.
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.	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.	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 *FIBRYGA* or additional infusions, not originally anticipated for the type
Moderate	Incomplete cessation of bleeding and additional hemostatic intervention	Intra-operative blood loss was higher than maximal expected blood loss for the type of procedure performed	Some post-operative bleeding and oozing that was not due to complications of
	required, as clinically assessed by the treating physician; and/or between 20 and 25% drop in hemoglobin compared to pre-infusion.	in a subject with normal hemostasis, but hemostasis was controlled.	surgery; control of post- operative bleeding required increased dosing with *FIBRYGA* or additional infusions, not originally anticipated for the type of procedure.

None	No cessation of bleeding and alternative hemostatic intervention required, as clinically assessed by the treating physician; and/or >25% drop in hemoglobin	Hemostasis was uncontrolled necessitating a change in clotting factor replacement regimen.	Extensive uncontrolled post-operative bleeding and oozing. Control of postoperative bleeding required use of an alternate fibrinogen concentrate.

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 occur with minor bleeding, thus absence of a drop in hemoglobin would not be an acceptable measure of hemostasis in such instances. 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. In the original memorandum, there was mention of discussions between the Agency and the Applicant to optimize the objective capture of hemostatic responses. This issue has not been completely resolved, and review of hemostatic data continues to demand significant adjudication, and multiple information requests.

Table 14 Post operative hemosatic assessment

Intra-operative assessmen	**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 Adjudicatio	Failure	Failure	Failure

The final efficacy assessment for each subject was adjudicated by the Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC). (Source: Table 9 CSR page 30)

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was originally defined as the hemostatic success of the first BE of each treated subject. As in FORMA 04, we considered the hemostatic success of all BEs, rather first BEs as the efficacy endpoint.

Hemostatic Efficacy data from FORMA 02 were reviewed previously for licensing in a 2017 interim analysis which included 23 minor BE outcomes occurring amongst 11 subjects. No Major BEs occurred prior to the data cut-off, thus none were included for analysis. One BE was determined by the Agency to be a major protocol deviation and was removed from the analysis set (FIBRYGA was substantially underdosed and laboratory data submitted revealed negligible change in fibrinogen level or MCF, therefore, any hemostatic activity was clearly independent of FIBRYGA).

Subsequent to 2017, a total 24 subjects were treated for 87 evaluable BEs. Besides the one BE excluded for major protocol deviation in the interim analysis, one of the minor BEs subsequently was also excluded as it is uninterpretable (details below in discussion of minor BEs).

Major BEs are more informative of efficacy and will be discussed first. According to the Applicant, two subjects were treated for major BEs on study; however in the judgement of this reviewer one did not meet the criteria for being major. Subject (b) (6) was treated for occult GI bleed, but lacked features of a major BE based on available clinical documentation. The subject maintained normal systolic blood pressure (100-110 mmHg) and pulse (70s-84s) and though diastolic pressure occasionally dropped to 60 mmHg, IV fluid was not required until the 3rd day. Additionally, hemoglobin level decreased by 11% (< the 20% criterion for a major BE).

Subject (b) (6) was treated for intracranial hemorrhage (ICH), which was considered a major BE following a presentation of 5 days of headache, right eye pain, one bout of emesis, and brain MRI positive for encephalomalacia of the right occipital lobe and hemorrhage in the right occipital region. The Baseline fibrinogen level was <10 mg/dl. A FIBRYGA dose of 102.6 mg/dl was infused although the protocol specified FIBRYGA dose was 83 mg/kg. Fibrinogen levels were: 204 mg/dl1-h post infusion and 199 mg/dl 3-h post infusion. He did not require additional infusions until Day 5, as his level was 154, 142, 99 and 0 mg/dl, on days 2, 3, 4, and 5, respectively. He still had a headache on Day 2, which improved to mild by Day 3. The subject's symptoms completely resolved by Day 4. On Day 7, the repeat brain MRI showed no progressive bleeding or changes since the previous scan and was read as cessation of hemorrhage. He was discharged and denied any complaint at follow-up on Days 14 and 30. Hemostatic efficacy was rated as good per the investigator and excellent by IDMEAC.

Given that his presenting symptoms resolved by Day 4, and cessation of bleeding was further confirmed by imaging on Day 7, this reviewer considers the hemostatic efficacy rating as good, consistent with eventual but not immediate cessation of bleeding.

Minor BEs:

The minor BEs included mild hemarthrosis or superficial muscle, soft tissue or dental, vaginal and GI bleeding. Minor BEs were reviewed in the context of concomitant medications, vital signs and hemoglobin levels, as well as doses of FIBRYGA vs achievement of target fibrinogen levels, and maximal clot firmness (MCF). Clinical

narratives describing daily hemostatic and general outcomes by investigator as well as hemostatic scores given to each BE by the investigator and by IDMEAC were scrutinized. The Investigator and IDMEAC adjudicated scores were in agreement except in 19 cases of discrepancies. These were further reviewed and adjudicated by this reviewer.

Both the investigator and IDMEAC rated the 7th BE for Subject (b) (6) as excellent hemostasis; however, as no clinical data were provided to substantiate the score, the BE was removed from analysis as uninterpretable. The number of evaluable BEs therefore is 87, one major, and 86 minor. Of these 87 BEs, one subject was treated for 27 BEs, and another for 10 BEs.

In general, subjects treated for minor BEs achieved target fibrinogen levels, and had a substantial rise in MCF following the Day 1 FIBRYGA infusion.
However, in the case of Subject (b) (6), when treated for her 5th BE (thigh hematoma) the local laboratory fibrinogen level was 172 mg/dl, but the central laboratory level was 83 mg/dl. Her MCF did not rise (remained zero mm), but she was noted to have achieved excellent hemostasis. In this case, it is possible that the zero MCF was erroneous, but given the fibrinogen level only barely above the 80 mg/dl lower end of the target range, spontaneous hemostasis (independent of treatment effect) is a possibility. Similarly, in the 5th BE for Subject (b) (6), the central laboratory fibrinogen level was 81mg/dl and the MCF did not rise (was 0 mm). In this case, due to hemoglobin dropping over 10%, the hemostatic score was good, not excellent. On the other hand, in subject (b) (6) 3rd BE, the post infusion fibrinogen level rose to 79 mg/dl (slightly below the lower end of the target level), with the MCF rising to 4mm, and documentation of excellent hemostasis. In the same subject's 5th BE, the fibrinogen level documented at the central laboratory rose to 76 mg/dl at 1 h post-infusion and the MCF remained at 0mm, and he was documented with a good/excellent hemostasis score. For the 4 h BE of Subject (b) (6) (menorrhagia), the central fibrinogen level rose only to 79 mg/dl, though she achieved a good rise in the MCF to 4 mm, but she achieved a moderate score (failure). Subject (b) (6) for the 2nd BE, a thorax hematoma, had a rise in the fibrinogen level at the local lab to 105 mg/dl at 1h and a MCF rise to 4 mm. However, the central lab reported a level of 0 mg/dl fibrinogen (likely laboratory error), although the score was rated as excellent.

Reviewer's comment:
Minor BEs tended to have excellent hemostatic outcomes, with only one BE considered a failure (moderate hemostatic score). However, among successfully treated minor BEs, in a few cases, the fibrinogen level achieved at 1 h post infusion was close to the lower target range, and the functional surrogate of thrombosis, maximal clot firmness, was not increased by infusion of FIBRYGA, therefore, the hemostasis achieved might have been in part independent of treatment effect.

The single major BE treated on FORMA 02 was a subject with ICH infused with a supra-protocol dose, and whose fibrinogen level rose to greater than target level of 204 mg/dl. His hemostatic score was only good as adjudicated by this reviewer given the dosing irregularity and limits the generalizability to major BE. While intracranial bleeds are appropriately considered major BEs, and can have devastating long-term sequelae, their treatment in patients with CFD is not fully generalizable to other types of major BEs, such as extensive traumatic bleeds, or large intramuscular and soft tissue bleeds. In these bleeding scenarios,

significant and ongoing consumption of fibrinogen would necessitate more frequent, larger FIBBRYGA doses to be administered, based on the fibrinogen level.

This major BE (intracranial hemorrhage) was successfully managed with FIBRYGA (hemostatic efficacy score of good), although the subject's hemostasis was eventual rather than immediate. This case does illustrate that despite achieving excellent target fibrinogen levels, in some cases hemostasis is somewhat delayed. Such degree of imperfect correlation between achieved fibrinogen levels vs. hemostatic outcomes was also noted for perioperative management (see below). Overall success rate for treatment of major BEs in FORMA 02 is 100%.

6.2.11.2 Analyses of Secondary Endpoints

Hemostatic efficacy in perioperative management

Nine subjects (two of whom also were treated for BE) underwent 12 surgeries. One surgery was major (right eye enucleation and socket reconstruction) and the remainder were minor. Each subject was infused within 3 hours before surgery. Efficacy assessments using four-point scales were performed by the surgeon at the end of the procedure, by a hematologist after the surgery, and data were adjudicated by IDMEAC.

Table 15 Surgical procedures FORMA 02

Subject Identifier	Reported Name of Procedure
FORMA_02-(b) (6)	1.Radio Isotope Synovectomy (Left Knee) (Intra-articular Isotope Injection)
FORMA_02-	2. Tooth Extraction
FORMA_02-	3. Radio Isotope Synovectomy (Left Knee) (Intra-articular Isotope Injection)
FORMA_02-	Root Canal Operation
FORMA_02-	Dental Extraction
FORMA_02-	1.Circumcision
FORMA_02-	2.Excision of scar bud of circumcision
FORMA_02-	Circumcision
FORMA_02-	Extraction of Tooth 36 dental scaling
FORMA_02-	Right eye enucleation with socket reconstruction*
FORMA_02-	Skin Biopsy
FORMA_02-	Debridement - superficial necrosis Lt. third toe

*Major surgery (Source: 125612.67 PR.xpt dataset)

Intraoperative hemostatic efficacy assessment: Treatment was assessed as successful in all subjects (rating of excellent in 11 (91.7%) surgeries or good in 1 (8.3%) of surgeries (90% CI 0.816 to 1.0). Efficacy of all minor surgeries was excellent, and efficacy was rated as good in the one major surgery. The surgeons and the IDMEAC agreed in all cases.

Postoperative assessment: The hematologists assessed the success as 100% for all 12 procedures (90% CI 0.816 to 1.0). The IDMEAC rated the efficacy as excellent for the three minor surgeries and good for the major surgery.

The sole major surgery ((b) (6)), had intra and post-operative hemostasis assessed as good by surgeon, hematologist and IDMEAC, with delayed oozing and bleeding on Days

2 and 3. Please refer to original 2017 review memorandum for details, however there was a substantial dosing discrepancy between the FIBRYGA dose calculated per protocol, and the dose the subject actually received before surgery on Day 1. His per protocol calculated dose is 78 mg/kg, but he received 103 mg/kg. His operative level reached 220 mg/dl, exceeding the target level and guidelines.

(b) (4)

Five of the minor surgeries required maintenance doses, median number was 3 (range 1-4). Hemostatic success was defined as achieving a hemostatic efficacy grade of excellent or good, and thus the hemostatic success rate was 100% in these 12 surgical events. Three surgical cases were previously reviewed in detail, please see the previous 2017 memorandum for Subjects (b) (6) . Subject (b) (6) had two additional surgeries, the first occurring before the interim report in 2017.

FIBRYGA dose irregularities also occurred with minor surgeries. For example, during the first surgery in Subject (b) (6), the protocol dose was 55.5 mg/kg, but 70 mg/kg was infused. Despite this, the 1h post infusion fibrinogen level failed to reach target of 100 mg/dl, rising from 0 to 59 mg/dl. The surgery was delayed until a second infusion elevated his fibrinogen level to 85 mg/dl. His surgery was subsequently successfully completed. He received a third dose on the day after surgery, per protocol.

During his second minor surgery, which was another knee surgery, he had a baseline fibrinogen level of 0 mg/dl. Although the protocol specified formula dose was 55.5mg/kg, he was infused with 74 mg/kg. His fibrinogen level rose to 75 mg/dl intraoperatively.

During his 3rd minor surgery, his baseline level was again 0 mg/dl. To achieve a target level of 100 mg/dl, he was dosed with 72 mg/dl although the protocol specified dose was 55.5mg/kg. Due to a subtherapeutic fibrinogen level, he was given a second infusion which brought up his level to 82 mg/dl and then he proceeded to surgery.

In addition to these irregularities, there were a number of subjects with dose discrepancies where each received substantially more FIBRYGA than the protocol formula stipulated, of which one, Subject (b) (6), was given 2.3 times the protocol specified dose. These are listed in Table 17.

Table 16 FORMA 02 Perioperative Management Dosing Discrepancies

Subject ID	1h post infusion fibrinogen level (mg/dl)	Target fibrinogen level (mg/dl)	Baseline fibrinogen level (mg/dl)	Investigator FIBRYGA dose (mg/kg)	Reviewer/protocol FIBRYGA dose (mg/dl)
(b) (6)	164	100	0	69.77	55.5
	96	100	0	58.46	55.5
*	111	100	0	61.11	55.5
	112	100	0	65.79	55.5
	105	100	0	127.91	55.5
	84	100	10	66.05	50

(b) (6)	162	100	0	66.15	55.5

*subject had a second surgery

(b) (4)

6.2.11.3 Subpopulation Analyses

None. Sample sizes insufficient to conduct clinically meaningful analyses.

6.2.11.4 Dropouts and/or Discontinuations

Not applicable

6.2.11.5 Exploratory and Post Hoc Analyses

Not applicable

6.2.12 Safety Analyses

6.2.12.1 Methods

All 25 treated subjects are included in the safety population and were given a total of 131 infusions of FIBRYGA. A total of 91 AEs occurred in 19 (76%) subjects, of which 43 AEs in 15 subjects were TEAEs.

TEAEs were defined as AEs that occurred from the start of the FIBRYGA infusion until Day 30. Safety labs were obtained, and physical examinations were done at multiple time points (see Appendix). At each scheduled or unscheduled visit, AEs were actively solicited using non-leading questions. The investigator assessed all AEs as mild, moderate or severe, and serious or non-serious, as well as causality. Clinically significant laboratory abnormalities were repeated and followed until return to normal and/or an adequate explanation was available. Safety data were categorized using MedDRA version 18.1.

Severity of the AE was categorized as:

- Mild: transient and causes discomfort but does not interfere with the subject's routine activities.
- Moderate: sufficiently discomforting to interfere with the subject's routine activities
- Severe: Incapacitating and prevents pursuit of subject's routine activities

6.2.12.2 Overview of Adverse Events

Adverse events are summarized in Tables 18 and 19 below.

Table 17 Summary of Severity of all AEs (Safety population, N=25)

Severity	Number/relatedness
Severe	10 (not related)
Moderate	23 (one possibly related)
Mild	58 (one possibly related)

(Source: Derived from Dataset AE.XPT in submission 125612/67)

Table 18 AEs Occurring in More Than One Subject During FORMA 02 (N=25)

	N	%
Limb injury	3	5.1
Extremity pain	3	5.1
Limb injury	3	4.6
Arthralgia	2	3.3
Hypertension	2	3.3
Iron deficiency anemia	2	3.3

(Source: Reviewer's compilation of data from sBLA 125612/67, 5.3.5.2 Data Tabulation Dataset SDTM, dataset AE). Aes consisting of bleeding were not counted as they are/can be considered as treatment failures.

AEs related to study drug:
Three AEs were categorized as likely related to study drug as per reviewer adjudication. One AE categorized as possibly related to the study drug was a drug eruption described in detail in the 2017 prior review memorandum and will not be further discussed here.

Subject (b) (6), developed symptomatic foot ischemia due to digital microthrombi after administration of FIBRYGA which was biopsy-proven, and required therapy. Note that this AE was also considered a serious adverse event (SAE) and a detailed description is provided in Section 6.1.12.4). Subject (b) (6) was described as having poor venous access, and during treatment of his second BE, developed an upper extremity phlebitis at the site of blood draw, which subsided 24h after the AE was discovered. This reviewer attributes both of these AEs to study treatment.

6.2.12.3 Deaths

None reported

6.2.12.4 Nonfatal Serious Adverse Events

There were 15 serious AEs in FORMA 02, which included: Hepatitis C relapse, anterior cruciate ligament tear, patellar fracture, accelerated hypertension, intracranial hemorrhage, ankle sprain, Dengue fever, hypocalcemia, iron deficiency anemia, thrombosis, transfusion reaction, upper gastrointestinal bleeding, spontaneous abortion, and peripheral ischemia.

Descriptions of SAEs:
The SAEs occurred in 5 subjects, and these are summarized below.
There were 3 serious SAEs reported in Subject #(b) (6), a 30-year-old White, non-Hispanic male, with history of chronic hepatitis C (HCV) infection who had 27 BEs treated during the study. After completing his 9th BE treatment, he stumbled and fell, suffering a traumatic cruciate ligament rupture and patellar fracture which required surgical repair (two SAEs). These resolved without sequelae and were assessed by the investigator as not related to FIBRYGA. Several months later, he had HCV reactivation that required hospitalization, which was his third SAE, determined as not related to FIBRYGA by the investigator. He recovered following treatment.

Subject (b) (6) also had three SAEs. A 19-year-old Asian male with a one-year history of chronic buphthalmos of the right eye was infused with FIBRYGA preoperatively for enucleation with eye socket reconstruction. About 1.6 years later, he experienced a traumatic right ankle sprain. He subsequently was evaluated at a hospital and diagnosed with accelerated HTN, (190/140mmHg) and treated. Both SAEs, ankle sprain and accelerated HTN were determined as not related to study drug. Lastly, he was admitted to the hospital with a 5-day duration headache, and MRI showed an intracranial hemorrhage. This was treated with FIBRYGA in the study, and a repeat MRI showed no worsening of the hemorrhage. The headache resolved and this SAE was determined not to be related to FIBRYGA by the investigator.

Subject (b) (6) had 7 SAEs. This subject is a 32-year-old female with a two-year history of anemia and erosive gastritis who was treated with FIBRYGA for a minor BE. During an admission, she had four SAEs: iron deficiency, upper gastrointestinal bleed (GIB), also mild hypocalcemia and Dengue fever. Endoscopy was normal. She was discharged and the investigator determined that the AEs were unrelated to FIBRYGA. Several months later, she was admitted to hospital with severe iron deficiency anemia from menorrhagia and treated with FIBRYGA followed by PRBC transfusion. Her hospital course was complicated by a moderate transfusion reaction with the 2nd unit. She received an additional transfusion and was discharged following resolution of her SAEs. Anemia and transfusion reaction were deemed unrelated to FIBRYGA. Three days later, she was admitted with menses and abdominal pain and was infused with FIBRYGA daily for minor a BE. However, on the 3rd day, the subject developed a brown discoloration and pain in the right toes. Laboratory and imaging evaluation was unrevealing, and skin biopsy was done (minor surgery, treated with FIBRYGA). Biopsy showed coagulative necrosis with microvesicular microthrombi. She was diagnosed with an SAE of ischemia due to digital microthromobi (PT thrombosis) and was discharged from hospital. About three weeks later, telephone follow-up documented that the symptoms had resolved. The Applicant assessed the SAE (thrombosis) as possibly related to FIBRYGA.

Subject (b) (6) was a 27-year-old Asian female who received a FIBRYGA dose for minor BE (gum bleeding). Urine pregnancy test at baseline was negative, but four and a half

months later, she reported a positive pregnancy urine home test, but then had spontaneous bleeding and did not seek medical help. This spontaneous abortion was categorized by the investigator as serious and severe, but unrelated to FIBRYGA.

Subject (b) (6) was a 26-year-old Asian male with left foot toe discoloration for about 2 months before admission to the hospital for bleeding and pain with purulent discharge of his left 3rd and 5th toe. He was treated for a minor toe bleed with FIBRYGA and underwent extensive imaging and serology evaluation, which was unremarkable. Diagnosis was empirically made as exacerbation of previous ischemia due to digital microthrombi. He underwent debridement surgery with perioperative FIBRYGA prophylaxis. About 21 days later, he was re-admitted for a week for pain in his left foot and received symptomatic treatment and was discharged. Per last follow up, a telephone visit a month later, the subject reported that the pain was reduced, and the investigator determined the SAE as recovered/resolved. This was categorized as not related to FIBRYGA.

Reviewer's comment:
Most of the AEs in the study were unrelated to study product, with the exception of a hypersensitivity skin reaction (AE was discussed in 2017, please refer to prior review memorandum), phlebitis (which did not require specific therapy nor cause significant symptoms to the subject, and resolved spontaneously), and thrombosis (please see below under SAE).

Most of the serious AEs occurring in this study appear unrelated to study product and include conditions such as accelerated hypertension, patellar fracture, iron deficiency anemia, spontaneous abortion, and purulent skin lesion discharge. The thrombotic SAE experienced by Subject (b) (6) in June 2017, where she received two doses of FIBRYGA while hospitalized with vaginal bleed, and developed peripheral ischemia is most likely related, and concerning, since the underlying fibrinogen deficiency and iatrogenic provision of fibrinogen can provoke thrombosis. This subject achieved target levels of approximately 100mg/dl as recommended. Her AE resolved with aspirin therapy. Her case does demonstrate the need for clinicians treating patients with CFD to be vigilant of signs and symptoms of thromboses and also further supports the necessity to further study this risk rigorously, such as with the ongoing PMR safety study.

6.2.12.5 Adverse Events of Special Interest (AESI)

A hypersensitivity reaction occurred in Subject (b) (6); please see prior 2017 review memorandum for a detailed description.

Subject (b) (6) developed peripheral phlebitis of upper limbs after FIBRYGA infusion, which resolved without treatment. The Applicant considered it possibly related to IMP, with which this reviewer agrees. The AE occurred a day after she was infused with FIBRYGA for her third BE.

6.2.12.6 Clinical Test Results

In FORMA 02, seven of the 25 subjects in the safety population had at least one platelet count over 400k (thrombocytosis); however, these were clinically insignificant and all under 470K. Most of the subjects had documentation of anemia, iron deficiency, and

Subjects (b) (6) had history of splenectomy. Asplenia is a known cause of chronic thrombocytosis. All the cases were grade 1, asymptomatic laboratory findings.

Biomarkers of thrombogenicity

Several subjects had elevated prothrombin F1+F2 levels at baseline and several measurements outside of the range and after infusion of FIBRYGA. Of those who had normal values at pre-infusion, one subject treated for bleeding (#(b) (6)) had elevated prothrombin F1+F2 at 3 hours post infusion for treatment of the 12th, 19th and 24th BEs and at 1 hour after infusion for treatment of the 22nd BE. An additional subject with normal levels pre-infusion (#(b) (6), BE#1) displayed elevated levels of prothrombin F1+F2 at 1 day after the last infusion. Subject #(b) (6) during BE#5 also displayed elevated levels 1 day after the last infusion, and also had an elevated level (1200 pmol/L) at 1-hour post-infusion for treatment of the seventh BE. By 3 hours post-infusion the level had decreased to 591 pmol/L; however, this remained above the upper limit of the reference range (229 pmol/L). Subject (b) (6) developed an AE of thrombosis in the study and had elevated levels during all 4 BEs, and perioperatively.

D-dimer was also monitored.
Subject (b) (6), who developed the SAE of thrombosis during treatment of her 4th BE, had an elevated level of 88 micrograms/l at 1 h post infusion, which rose to 4400micrograms/l on the day after the last infusion, when she developed painful discoloration of the toes. Two subjects had D-dimer elevations during perioperative management.

Reviewer's Comment: Measurement of prothrombin fragment F1+F2 and D-dimer levels are used as noninvasive screening tests for thrombosis. While the tests are not entirely specific, and most subjects who had elevated levels did not suffer thrombosis during the study, one subject did have elevations of both prothrombin fragments F1+F2 and D-dimer and did develop extremity thrombosis following infusions of FIBRYGA.

The laboratory analyses for Prothrombin fragment F1+F2 required 4 to 9 days for report of results, limiting its clinical utility in acutely bleeding patients.
D-dimer has only moderate specificity, especially among surgical patients, limiting its utility. Given the paradoxical propensity of patients with CFD to develop thromboses, clinicians will need to have a high index of clinical suspicion while treating subjects. Furthermore, the PMR safety study will provide additional data to evaluate thrombotic risks. The product label notifies the prescriber of this risk in Warnings and Precautions as well as Adverse Reactions section and instructs users to report suspected adverse reactions to the Agency.

Immunogenicity
Anti-fibrinogen antibodies were detected in 6 subjects. In three of these, the antibodies were already detected at Day 1 prior to the first FIBRYGA infusion. In the other three subjects, antibodies developed during the study. For one of these subjects, these were still present at the end of the study, while for the other two subjects the test normalized before end of the study. In the cases where the test indicated the presence of de novo antibodies, these did not appear to be neutralizing as there was no observable effect on fibrinogen levels or efficacy.

Reviewer's Comments: Anti fibrinogen antibodies are known to occur with FRT, however, their clinical significance is unclear, and the testing platform is (b) (4) **. Therefore, at this time, the reviewer does not recommend adding warnings for the possibility of development of anti-fibrinogen antibodies in the Warnings and Precautions section of the PI.**

6.2.12.7 Dropouts and/or Discontinuations

No subjects discontinued the study prematurely because of an AE.

6.2.13 Study Summary and Conclusions

FORMA 02 provided additional safety data substantiating the use of FIBRYGA in adolescents and adults for treatment of bleeding events. (b) (4)

(b) (4)

7. INTEGRATED OVERVIEW OF EFFICACY

An integrated summary of efficacy was only conducted for the perioperative management of BEs in CFD.

7.1 Indication #1

On-demand bleeding treatment in children, adolescents and adults.

7.1.1 Methods of Integration

Because FIBRYGA is already approved for on-demand treatment in adolescents and adults with CFD, data supporting the proposed indication for on-demand treatment in children presented in this supplement was reviewed separately as documented in Section 6 of the review. (i.e. not reviewed using integration of the two studies).

7.1.2 Demographics and Baseline Characteristics

Not Applicable

7.1.3 Subject Disposition

Not Applicable

7.1.4 Analysis of Primary Endpoint(s)

Not Applicable

7.1.5 Analysis of Secondary Endpoint(s)

Not Applicable

7.1.6 Other Endpoints

Not Applicable

7.1.7 Subpopulations

Not Applicable

7.1.8 Persistence of Efficacy

Not applicable

7.1.9 Product-Product Interactions

Not Applicable

7.1.10 Additional Efficacy Issues/Analyses

Not Applicable

7.1.11 Efficacy Conclusions

Not Applicable.

7.2 Indication #2

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Safety data from FORMA 02 and FORMA 04 were categorized using MedDRA version 18.1. Adverse events (AEs) were categorized as mild, moderate or severe. Due to significantly different participant different age categories, integrated safety analysis of FORMA 02 and FORMA 04 would not be very informative.
We performed an integrated safety review of the subpopulations (perioperative management and on-demand bleeding treatment) within each study. This is because within each of the studies both of these subpopulations were exposed to similar FIBRYBA dose and similar schedule, along with comparable safety monitoring regimes. Furthermore, surgery and spontaneous or traumatic hemorrhage in subjects with CFD share the pathophysiology of deficient fibrinogen, replaced with FIBRYGA.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was assessed in both FORMA 02 and FORMA 04. Safety data were adjudicated by an independent data monitoring and endpoint adjudication committee (IDMEAC)

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 25 subjects in FORMA 02 were exposed to at least one dose of FIBRYGA for on demand bleeding treatment or perioperative management. This population had the following demographics: 5 Asians, one Arab and 19 Whites. 11 Females and 14 males, Age range 12 to 49 years old. These subjects were infused with 131 infusions and a mean dose of 283.36mg/kg, per applicant in Study report.

A total of 9 subjects in FORMA 04 were infused with at least one dose of FIBYRGA to treat BEs or for perioperative management. Demographics of this population were as follows: 6 females and 3 males, 7 White and 2 Asian, Age ranged from 1 to 10 years old. These subjects received 21 doses of FIBRYGA. Per Applicant, the mean dose per subject in FORMA 04 was 174.6 mg/kg. (Source, study report).

8.2.3 Categorization of Adverse Events

All serious and non-serious AE were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1. AEs occurring between the start of the first FIBRYGA infusion and the end of each 30-day observation and follow-up period and during the surgical follow-up were recorded as treatment-emergent adverse events (TEAEs).

A total of 91 AEs were reported in 19 subjects treated for BE and perioperative management in FORMA 02. A total of 43 AEs in 15 subjects were TEAEs. Three AEs were classified as possibly or probably treatment related. (hypersensitivity reaction, phlebitis and digital ischemia). Fifteen serious AEs (SAEs) were reported in five subjects, of which one was characterized as possibly related to study drug (digital ischemia).

In FORMA 04, 10 AEs occurred in 4 subjects. Of these, 7 AEs in three patients were TEAEs. Two AEs in one patient (pyrexia and portal vein thrombosis) were assessed as possibly related to administration of fibryga and one was classified as an SAE (portal vein thrombosis). The numbers listed above were derived from the Applicant's Study Reports. However, they AEs were reviewed in safety review sections (6.1.12), (6.2.12.1) and were adjudicated and attributed by the reviewer.

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

Both FORMA 02 and FORMA 04 were open-label, single arm studies, and shared many features, including target dose of FIBRYGA administered. The studies primarily differed in the age of the study populations. Pooling across the subpopulations within each study has the caveats that management of surgery might differ from management of a bleed.

8.4 Safety Results

8.4.1 Deaths

None

8.4.2 Nonfatal Serious Adverse Events

FIBRYGA treated subjects in FORMA 02 and FORMA 04 had a total of 16 serious AEs occurring in 6 subjects, of which two, digital ischemia and portal vein thrombosis, were considered as possibly related to IMP.

The occurrence of SAEs of thromboses that are possibly attributable to the study drug in both studies stresses the importance of the ongoing safety PMR study focusing on the thrombotic risk among patients with CFD treated with FIBRYGA.

8.4.3 Study Dropouts/Discontinuations

A single subject from FORMA 04 was discontinued from study after developing the SAE of portal vein thrombosis, which occurred following splenectomy after splenic rupture and intraperitoneal hemorrhage. He was infused with several doses of FIBRYGA over a two-week period before the SAE was diagnosed. Splenectomy is associated with portal vein thrombosis, though infusions with FIBRYGA likely played a role and the applicant correctly ascribed the SAE as possibly related. The SAE was considered unresolved, though the subject was started on standard therapy with anticoagulant.

This thrombotic event in a five-year-old subject exemplifies the age-agnostic nature of thrombotic risk in patients with CFD. This reviewer supports inclusion of pediatric subject like this one into the ongoing safety PMR study.

8.4.4 Common Adverse Events

The most common AEs observed in subjects treated with FIBRYGA in both clinical studies included: nausea, vomiting, fever and thrombocytosis. A case of mild skin reaction (pruritus and erythema) occurred in one subject infused to treat a BE, who responded to therapy for hypersensitivity reactions, and the subject was able to tolerate FIBRYGA at a later date with prophylactic administration of medications for hypersensitivity reactions.

8.4.5 Clinical Test Results

The main clinical test finding was the asymptomatic laboratory abnormality of thrombocytosis in a pediatric subject in FORMA 04 after splenectomy whose platelet count reached over 2 x the upper limit of normal. This reviewer believes that while most likely the AE is a reactive process due to splenectomy and hemorrhage, given absence of follow up platelet results, some attribution to IMP cannot be excluded. In the adult/adolescent study, 7 subjects had platelet counts slightly above the upper limit of normal range, with no symptoms or sequelae.

8.4.6 Systemic Adverse Events

None

8.4.7 Local Reactogenicity

Not Applicable

8.4.8 Adverse Events of Special Interest

Thrombosis is a known, paradoxical complication seen among up to 5 % of subjects with CFD, and this risk might be potentiated by augmentation of fibrinogen. Of 34 subjects in the combined safety populations in FORMA 02 and 04, receiving a total of 167 dose of FIBRYGA exposure, two (5.9%) subjects experienced thrombosis.

This reviewer recommends that subjects under 12 years of age be included in the ongoing safety PMR study of this risk (currently planning to enroll subjects 12 and above).

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not Applicable

8.5.2 Time Dependency for Adverse Events

Not Applicable

8.5.3 Product-Demographic Interactions

Not Applicable

8.5.4 Product-Disease Interactions

Not Applicable

8.5.5 Product-Product Interactions

Not Applicable

8.5.6 Human Carcinogenicity

Not Applicable

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable

8.5.8 Immunogenicity (Safety)

Both studies in this supplement screened for anti-fibrinogen antibodies at baseline, and following treatment with FIBRYGA. There were 3 cases of preexisting antibodies and one case of de novo antibodies. In all four cases, these findings did not impact hemostatic efficacy nor affect dose response characteristics. Anti-fibrinogen antibodies have also been noted with use of other fibrinogen replacement products, but no fibrinogen inhibiting antibodies to fibrinogen supplementation therapy have been reported.

8.5.9 Person-to-Person Transmission, Shedding
Not Applicable

8.6 Safety Conclusions

Safety of FIBRYGA therapy was evaluated in both FORMA 02 and FORMA 04 studies. Please see sections 6.1.12.2 and 6.2.12.2 for more detailed analysis. The most significant concern is thrombosis which was seen in one subject in each study, classified as possibly related to FIBRYGA. Concerns regarding thrombosis are the basis for the recommended PMR safety study focusing on thrombotic risk. The integrated safety analysis identifies no new safety concerns except possibly thrombocytosis. While this case of thrombocytosis is likely reactive and related to splenectomy, the subject was discontinued from the study for portal vein thrombosis and no follow up platelet data were available to potentially demonstrate improvement or resolution, therefore, this AE is considered possibly related to FIBGRYGA. No deaths were reported in the studies. A small number of anti-fibrinogen antibodies were detected, of which most were pre-existing, with no evidence of inhibiting fibrinogen activity. Therefore, the safety profile based on the results of the pooled analysis of FORMA 02 and 04 of Fibryga supports the conclusion that the benefit-risk profile favors approval of FIBRYGA in children < 12 years old for the treatment of BEs.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

Not Applicable

9.1.1 Human Reproduction and Pregnancy Data

Not Applicable

9.1.2 Use During Lactation

Not Applicable

9.1.3 Pediatric Use and PREA Considerations

This submission fulfils the PREA postmarketing requirements for FIBRYGA for the treatment of bleeding episodes. The submitted efficacy data supports extending the indication for the treatment of bleeding events to patients with CFD under age 12 years old. The safety data from FORMA 04 and published literature show that children share the thrombotic risk seen in adolescents and adults with FRT. Therefore, this reviewer recommends enrollment of subjects <12 years of age in the ongoing PMR#1 safety study, which currently plans to enroll subjects aged 12 and above.

9.1.4 Immunocompromised Patients

Not Applicable

9.1.5 Geriatric Use

Not Applicable

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

Not Applicable

10. CONCLUSIONS

Efficacy data in this supplement support granting the indication of FIBRYGA for treatment of bleeding events in pediatric subjects <12 years of age with congenital fibrinogen deficiency. This recommendation rests on the totality of data, including that previously reviewed for licensing, as well the completed FORMA 02 study in adults and adolescents. PK data generated in FORMA 04 demonstrated faster clearance and shorter FIBRYGA half-life in children compared with adults/adolescents leading to important dosing modification. If the baseline fibrinogen level is known, a pediatric (<12 years old) formula will now utilize an incremental IVR of 1.4 mg/dl/mg/kg, in contrast to 1.8 mg/dl/mg/kg recommended in the adult/adolescent population. The safety profile was favorable; however, two AEs of thrombosis, potentially related to FIBRYGA, were observed in subjects enrolled on FORMA 02 and 04. Subjects <12 years old will be added to the ongoing adult/adolescent safety PMR study to further evaluate this risk. Due to insufficient perioperative data especially in major surgery, this reviewer recommends against granting FIBRYGA for the indication of perioperative management of bleeding in patients with CFD.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Congenital fibrinogen deficiency (CFD) (Hypofibrinogenemia and Afibrinogenemia) are an extremely rare hereditary bleeding disorder characterized by bleeding complications that can lead to chronic impairment and deformities, as well as catastrophic complications like intracranial hemorrhage, if untreated. However, the bleeding rates are highly variable, furthermore, patients have a paradoxical propensity to arterial and venous thrombosis. • On-demand therapy with fibrinogen concentrate is generally recommended to minimize and prevent hemorrhagic sequelae and is the standard of care in most countries. • Prophylactic infusions of fibrinogen concentrates are often used off-label before elective surgery in patients with CFD	• CFD is a very rare disease • CFD can have debilitating impact on physical well-being. • CFD may lead to life threatening consequences if untreated.
Unmet Medical Need	• FIBRYGA and another fibrinogen concentrate have been licensed by the United States Food and Drug Administration (FDA) for treatment of CFD related bleeding events. • Plasma-derived fibrinogen concentrates carry risk of infection and hypersensitivity • Paradoxical hypercoagulable state in patients with CFD can be potentiated by administration, especially repeated, in cases of major bleeding events or major surgery.	• FIBRYGA utilizes multiple, advanced manufacturing processes to purify and standardize the product and inactivate most known infectious agents. • Thrombotic risks of exogenous fibrinogen concentrate are intrinsic to its mode of action.
Clinical Benefit	• FIBRYGA has been previously shown to have acceptable safety and sufficient efficacy to be approved for the on-demand treatment of BEs in adolescents and adults. • (b) (4) • Part of a pediatric study of on-demand bleeding event treatment with FIBRYGA in subjects ≤ 12 years old, evaluated a total of 2 minor and one	• Adequate efficacy data of FIBRYGA for bleeding event treatment were demonstrated in adolescent and adult subjects. • Adequate efficacy data of FIBRYGA for treatment of bleeding events in pediatric subjects ≤12 years old have been submitted.

	major surgical cases treated with FIBRYGA, all aged 0 to <6, and none in the pediatric age bracket of 6 to <12.	• (b) (4)
Risk	• The most substantial risks of fibrinogen concentrate products are development of thromboses. • In studies of FIBRYGA use for bleeding management and perioperative management perioperative management, thromboses were observed. In the study of FIBRYGA for perioperative management perioperative management, the thrombotic event was a serious adverse event, considered as possibly related to FIBRYGA and led to the discontinuation of the subject from study.	• Evidence suggests that infectious risks and hypersensitivity risks from FIBRYGA treatment are minor. • Risk of thrombosis with FIBRYGA us is sufficient for the agency to require a Postmarketing requirement study in bleeding treatment among subjects ages 12 and above. • (b) (4)
Risk Management	• The most substantial risk of treatment with fibrinogen concentrates are thrombotic events. • A postmarketing requirement study is ongoing, to further evaluated this risk in the bleeding treatment indication among adolescents and adults (ages 12 years old and above)	• FIBRYGA package insert, along with routine pharmacovigilance activities, are adequate to manage risk. • Postmarketing requirement study will be expanded to include subjects ≤12 years of age treated for bleeding events.

Insert table number and title here

11.2 Risk-Benefit Summary and Assessment

Data from FORMA 04 suggest that FIBRGYA treatment in children < 12 years of age leads to successful hemostasis, thus demonstrating its efficacy in this indication. Benefit/risk profile of FIBRYGA is considered favorable based on data from FOMRA 04 for treatment of bleeding episodes in subjects < 12 years of age.

(b) (4)

11.3 Discussion of Regulatory Options

In this efficacy supplement, the Applicant requested approval for the on-demand treatment of bleeding episodes in children < 12 years old, (b) (4) of patients with CFD.

The data are considered sufficient to support the approval of FIBRYGA for the on-demand bleeding indication in subjects < 12 years of age. (b) (4)

(b) (4)

(b) (4) the indication of bleeding treatment in subjects < 12 years of age, regulatory action is approval.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends expanding the indication for on demand treatment of acute bleeding episodes to pediatric patients < 12 years of age with congenital fibrinogen deficiency.

11.5 Labeling Review and Recommendations

This clinical reviewer recommends approval of labeling with changes as described in 11.4. (b) (4)

APLB has reviewed the label and the Applicant has acceptably addressed issues brought up by APLB the review team.

11.6 Recommendations on Postmarketing Actions

This submission fulfills the Applicant's PMR #1 identified in the June 7, 2017, approval letter for BLA STN BL 125612/0 for FIBRYGA, specifically:

- PMR #1: Deferred pediatric study under PREA for the treatment of acute bleeding in pediatric patients ages < 12 years of age with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.
  Final Protocol Submission: September 28, 2015
  Study Completion Date: December 31, 2020
  Final Report Submission: June 30, 2021

- PMR#2 a prospective observational study of patients ≥12 years of age with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYGA for at least 10 major bleeding events to further characterize the risk of thromboembolic events following FIBRYNA treatment. Timetable submitted by applicant on May 5, 2017 stipulates that the study will be conducted according to the following schedule:
  Final Protocol Submission: September 30, 2017
  Study Completion Date: March 31, 2024
  Final Report Submission: June 30, 2024

At the time of this efficacy submission, the PMR #2 study had not enrolled subjects and was withdrawn. It was replaced with a new version (3) of the study now also including subjects <12 years of age:

Open-label, uncontrolled, multicenter, observational study of subjects of any age with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYGA for at least 10 major bleeding events to further characterize the risk of thromboembolic events following FIBRYNA treatment.

Date of Protocol: 02 December 2020
Planned Clinical Start: 4th quarter 2020
Planned Clinical End: 4th quarter 2027.

APPENDIX

FORMA 02

FORMA 02 Subject observation schema charts
FORMA 02 Flow chart of assessments for on-demand treatment of acute bleeding

		30-DAY OBSERVATION AND FOLLOW-UP PERIOD												
		Day 1			All study days after Day 1			Day of Last Infusion			24 hours (i.e., 1 day) after last infusion or end of the observation period	Day 14 (±2 days)	Day 30 (±1 week)	Study completion visit
	Screening	Pre-infusion	Post-infusion		Treatment observation period (At least 3 days for minor bleeding and 7 days for major bleeding)			Pre-infusion	Post-infusion					
			1 h (±15 min)	3 h (±15 min)	Daily	Pre-infusion[a]	1 h (±15 min) post-infusion[a]		1 h (±15 min)	3 h (±15 min)				
Eligibility and informed consent	X	#												
Demography	X													
Medical history, review of previous therapy	X	X												
Physical examination		X									X		X	X
Vital signs		X	X	X			X		X	X	X			
Height and weight		X												
Characterisation of BE		X												
Blood drawn for:														
Fibrinogen activity		X[b, c, d]	X[c, d]	X[d]	X[c, d]	X[b, c, d]	X[c, d]	X[b, c, d]	X[c, d]	X[d]	X[d]			
Fibrinogen antigen		X[b, d]	X[d]	X[d]	X[d]	X[b, d]	X[d]	X[b, d]	X[d]	X[d]	X[d]			
MCF [d]		X[b]	X						X					
Thrombogenicity [d]		X	X	X			X		X	X	X			
Immunogenicity [d]		X										X	X	
Safety lab (haematology and clinical chemistry) [c]		X	X	X	X[f]		X		X	X	X			
Retention plasma samples [e]		X[b]	X	X	X	X	X	X	X	X	X	X	X	
Retention serum samples [e]		X[b]												X
Urine or blood pregnancy test		X												
Infusion of *Octafibrin*			X[f]			X[f, g]			X					
Final haemostatic efficacy assessment											X			
AEs [h]		>	>	>	>	>	>	>	>	>	>	>	>	>
Concomitant medications		>	>	>	>	>	>	>	>	>	>	>	>	>

AE = adverse event; BE = bleeding episode MCF = maximum clot firmness (clot strength).
# To be reviewed if period between screening and treatment is more than 3 months.
[a] If, based on daily assessment, the investigator considers an additional infusion of *Octafibrin* necessary (see footnote f).
[b] Within 30 minutes before infusion.
[c] Measured in local laboratories.
[d] Measured in central laboratory.
[e] Plasma retention sample for potential retesting: serum retention sample for potential viral testing.
[f] If the *Octafibrin* infusion administered on this day is deemed the only infusion needed for treatment of patient's BE, the post infusion assessments as detailed in the more comprehensive schedule for the Day of Last Infusion must be performed.
[g] If the actual fibrinogen plasma level is below the recommended lower limit of target fibrinogen plasma level, the patient should receive another infusion of *Octafibrin*. If the fibrinogen plasma level is greater than or equal to the recommended lower limit of the target fibrinogen plasma level, *Octafibrin* should not be administered.
[h] Including thromboembolic events or hypersensitivity reactions.
[i] Haematology only.

FORMA 02 Flow chart of assessment for perioperative prophylaxis

		SURGICAL OBSERVATION PERIOD											
		Before surgery		Day 1 Surgery			Any POP Day (i.e. up to but excluding either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever came later)			Last POP Day (i.e. either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever came later)			Study completion visit
	Screening	Within 12 h before start	Within 3 h before start	Start	Intra-operative	End	Daily	Pre-infusion	1 h post-infusion (±15 min)	Daily	Pre-infusion	1 h post-infusion (±15 min)	
Eligibility and informed consent	X	#											
Demography	X												
Medical history, review of previous therapy	X	X											
Details of surgery (location, type, severity)		X											
Estimated blood loss, duration of surgery, transfusion requirements		X											
Any planned ancillary therapy during the surgery (i.e. antifibrinolytics)		X											
Actual duration of surgery						X							
Details of hospitalization and follow-up (narrative)						X							
Actual blood loss and transfusion requirement						X							
Physical examination		X											X
Vital signs		X					X			X			
Body weight		X											
Blood drawn for:													
Fibrinogen activity			X[a, b, c]		X[a, b, c]	X[b, c]	X[b, c]	X+[b, c]	X[b, c]	X[b, c]	X+[b, c]	X[b, c]	
Fibrinogen antigen			X[a, c]		X[a, c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
Thrombogenicity [c]			X			X			X			X	
Safety lab (haematology and clinical chemistry) [b]		X					X		X	X		X	
Retention plasma samples [d]			X		X[g]	X	X	X	X	X	X	X	
Retention serum samples [d]			X										X
Urine or blood pregnancy test		X											
Infusion of *Octafibrin*			X		X**				X[h]			X[h]	
Haemostatic efficacy assessments (intra- and post-operative)						X[f]						X[g]	
Wound haematomas and oozing							X			X			
Narrative of Outcome												X	
AEs [h]			>	>	>	>	>	>	>	>	>	>	>
Concomitant medications		>	>	>	>	>	>	>	>	>	>	>	>

AE = adverse event; POP = post-operative
* ≤30 minutes before each infusion of *Octafibrin*.
** If considered necessary.
# To be re-reviewed if period between screening and treatment is more than 3 months.
[a] ≤30 minutes before and after each infusion of *Octafibrin*.
[b] Measured in local laboratories.
[c] Measured in central laboratory.
[d] Plasma retain sample for potential retesting: serum retain sample for potential viral testing.
[e] If the actual fibrinogen plasma level is below the recommended lower limit of target fibrinogen plasma level, the patient should receive another infusion of *Octafibrin*. If the fibrinogen plasma level is greater than or equal to the recommended lower limit of the target fibrinogen plasma level, *Octafibrin* should not be administered.
[f] Intra-operative efficacy assessment by surgeon.
[g] Post-operative efficacy assessment by haematologist.
[h] Including thromboembolic events and hypersensitivity reactions.

(Source: CSR FORMA 02 Pages 34-37)

FORMA 04 Subject observation schema charts

FORMA 04 Flow Chart of Assessments for Treatment of BEs

	Screening	14 day PK Phase within 14 days after screening [j]	On Demand Bleeding – OBSERVATION AND FOLLOW-UP PERIOD										
			Day 1			All study days after Day 1			Day of Last Infusion		24 hours (i.e., 1 day) after last infusion or end of the observation period	Day 30 (±1 week)	Study completion visit
			Pre-infusion	Post-infusion		Treatment observation period (At least 3 days for minor bleeding and 7 days for major bleeding)			Pre-infusion	Post-infusion 1 h (±15 min)			
				1 h (±15 min)	3 h (±15 min)	Daily	Pre-infusion[b]	1 h (±15 min) post-infusion[b] (±15 min)					
Eligibility and informed consent	X		#										
Demography	X												
Medical history, review of previous therapy	X		X										
Physical examination			X								X	X	X
Vital signs			X	X	X			X		X	X		
TEE questionnaire			X	X	X	X	X	X	X	X	X	X	X
Height and weight			X										
Characterisation of BE			X										
Blood drawn for:													
Fibrinogen activity			X[b, c, d]	X[b, d]	X[d]	X[b, d]	X[b, c, d]	X[b, d]	X[b, c, d]	X[b, d]	X[d]		
Fibrinogen antigen			X[b, d]	X[d]	X[d]	X[d]	X[b, d]	X[d]	X[b, d]	X[d]	X[d]		
MCF [d]			X[d]	X									
Thrombogenicity [d]			X		X		X	X					
Immunogenicity [d]			X									X	
Safety lab (haematology and clinical chemistry) [c]			X			X[f]							
Retention serum samples [e]												X	
Infusion of *Octafibrin*			X[f]				X[f, g]		X				
Final haemostatic efficacy assessment											X		
AEs [h]			>	>	>	>	>	>	>	>	>	>	
Concomitant medications			>	>	>	>	>	>	>	>	>	>	
Medical history since last study visit													X

AE = adverse event; BE = bleeding episode MCF = maximum clot firmness (clot strength); TEE, thromboembolic event.
# To be re-reviewed if period between screening and treatment is more than 3 months.
[a] If, based on the daily assessment, the investigator considers an additional infusion of *Octafibrin* necessary (see footnote f).
[b] Within 30 minutes before infusion.
[c] Measured in local laboratories.
[d] Measured in central laboratory.
[e] Serum retention sample for potential viral testing.
[f] If the *Octafibrin* infusion administered on this day is deemed the only infusion needed for treatment of patient's bleeding event, the post-infusion assessments as detailed in the more comprehensive schedule for the Day of Last Infusion must be performed.
[g] If the actual fibrinogen plasma level is below the accepted lower limit of target fibrinogen plasma level, the patient should receive another infusion of *Octafibrin*. If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* should not be administered.
[h] Including thromboembolic events or hypersensitivity reactions.
[i] Haematology only.
[j] Retention serum sample taken before PK infusion; PK infusion of 70 mg/kg of *Octafibrin*; subsequent blood sampling (see separate PK flow chart) (if not previously performed prior to a surgical procedure).

FORMA 04 Flow Chart of Assessment for Perioperative Prophylaxis

	Screening	14-day PK Phase within 14 days after screening [j]	SURGICAL OBSERVATION PERIOD											Study completion visit
			Before surgery		Day 1 Surgery			Any POP Day (i.e. up to and excluding either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever came later)			Last POP Day (i.e. either Day 4 for minor and Day 8 for major surgery or the day of the last post-operative infusion, whichever came later)			
			Within 12 h before start	Within 3 h before start	Start	Intra-operative	End	Daily[i]	Pre-infusion	1 h post-infusion (±15 min)	Daily[i]	Pre-infusion	1 h post-infusion (±15 min)	
Eligibility and informed consent	X		#											
Demography	X													
Medical history, review of previous therapy	X		X											
Details of surgery (location, type, severity)			X											
Estimated blood loss, duration of surgery, transfusion requirements			X											
Any planned ancillary therapy during the surgery (i.e., antifibrinolytics)			X											
Actual duration of surgery							X							
Details of hospitalisation and follow-up (narrative)							X							
Actual blood loss and transfusion requirement							X							
Physical examination			X											X
Vital signs			X					X		X	X		X	
TEE questionnaire			X				X	X	X	X	X	X	X	X
Body weight			X											
Blood drawn for:														
Fibrinogen activity				X[a, b, c]		X[a, b, c]	X[b, c]	X[b, c]	X*[b, c]	X[b, c]	X[b, c]	X*[b, c]	X[b, c]	
Fibrinogen antigen				X[a, c]		X[a, c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	
Safety lab (haematology and clinical chemistry) [b]				X				X			X			
Infusion of *Octafibrin*				X		X**				X[e]			X[e]	
Haemostatic efficacy assessments (intra- and post-operative)							X[f]						X[g]	
Wound haematomas and oozing								X			X			
Narrative of Outcome													X	
AEs [h]				>	>	>	>	>	>	>	>	>	>	
Concomitant medications			>	>	>	>	>	>	>	>	>	>	>	
Medical history since last study visit														X

AE = adverse event; POP = post-operative; TEE, thromboembolic event
* ≤30 minutes before each infusion of *Octafibrin*.
** If considered necessary.
# To be re-reviewed if period between screening and treatment is more than 3 months.

[a] ≤30 minutes before and after each infusion of *Octafibrin*.
[b] Measured in local laboratories.
[c] Measured in central laboratory.
[d] Plasma retain sample for potential retesting: serum retain sample for potential viral testing.
[e] If the actual fibrinogen plasma level is below the accepted lower limit of target fibrinogen plasma level, the patient should receive another infusion of *Octafibrin*. If the fibrinogen plasma level is greater than or equal to the accepted lower limit of the target fibrinogen plasma level, *Octafibrin* should not be administered.
[f] Intra-operative efficacy assessment by surgeon.
[g] Post-operative efficacy assessment by haematologist.
[h] Including thromboembolic events and hypersensitivity reactions.
[i] Only if no infusions given.
[j] Retention serum sample taken before PK infusion; PK infusion of 70 mg/kg of *Octafibrin*; subsequent blood sampling (see separate PK flow chart) (if not previously performed prior to a surgical procedure).

FORMA 04 Flow Chart of Assessment of PK portion of study

PK days		Vital signs	Fibrinogen ((b) (4) and Fib:Ag)[a]	Retention serum sample	Physical and clinical examination	Recording of AEs[b]
PK-Day 1*	Before first infusion	X	X[c]	X[d]		
	Single-dose infusion at a dose of 70 mg/kg					
	1 hour**	X	X			X
	3 hours**	X	X			X
PK-Day 2	24 hours**		X			X
PK-Day 4	72 hours**		X			X
PK-Day 7	144 hours**		X			X
PK-Day 10	216 hours**		X			X
PK-Day 14	312 hours**	X	X		X	X

[a] Measured in central laboratory.
[b] Including potential thromboembolic events and early signs of allergic or hypersensitivity reactions.
[c] Baseline fibrinogen for PK analysis ((b) (4) assay and (b) (4)) to be collected immediately prior to infusion of IMP.
[d] Collected within 30 min before infusion
* Before the start of the PK phase, there must be as least 2-week wash-out period of any fibrinogen containing product.
**Time relative to end of infusion.

(Source CRS pages 22-36)