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# BLA Clinical Review Memorandum

| | |
|---|---|
| Application Type | BLA Efficacy Supplement |
| STN | 125612/133 |
| CBER Received Date | 1/30/24 |
| PDUFA Goal Date | 7/31/24 |
| Division / Office | DCEH/OCE |
| Priority Review (Yes/No) | Yes |
| Reviewer Name(s) | Clinical Reviewers:<br>Megha Kaushal, MD, MSc<br>Courtney Johnson, MD<br>Clinical Pharmacology Reviewer:<br>Xiaofei Wang, Ph.D. |
| Review Completion Date / Stamped Date | 7/31/2024 |
| Supervisory Concurrence | 'Lola Fashoyin-Aje, MD, MPH |
| 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. | Lyophilized Powder for Reconstitution |
| Dosage Form(s) and Route(s) of Administration | Intravenous Use only after reconstitution |
| Dosing Regimen | Adults: The recommended dose is 4g<br>Adolescents 12 years of age and above: 50 mg/kg body weight<br>Children 0 to <12 years of age: 70 mg/kg body weight |
| Indication(s) and Intended Population(s) | Fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency |
| Orphan Designated (Yes/No) | No |

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GLOSSARY

| | |
|---|---|
| AE | adverse event |
| ABP | allogeneic blood product |
| CHF | congestive heart failure |
| CPB | cardiopulmonary bypass |
| CVA | cerebral vascular accident |
| DVT | deep venous thrombosis |
| ICU | intensive care unit |
| IDSMC | Independent Data Safety Monitoring Committee |
| IMP | Investigational Medicinal Product |
| MCF | maximum clot firmness |
| mITT | modified intent-to-treat |
| PI | prescribing information |
| PMP | pseudomyxoma peritonei |
| PT | prothrombin time |
| SAE | serious adverse event |
| sBLA | supplemental Biologics License Application |
| TEAE | treatment-emergent adverse event |
| TEE | thromboembolic event |

## 1. EXECUTIVE SUMMARY

On January 30, 2024, Octapharma (the Applicant submitted a supplemental Biologics License Application (sBLA) for FIBRYGA (Octafibrin), seeking approval for the following proposed indication and dosage:

- Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency:
    - For adults: 4g
    - For adolescents age ≥ 12 years: 50 mg/kg body weight
    - For children age <12 years: 70 mg/kg body weight

Acquired hypofibrinogenemia is a disorder that results in levels of circulating fibrinogen below normal values, typically <150mg/dL. Treatment for acquired hypofibrinogenemia includes treating the underlying cause along with fibrinogen replacement. Hypofibrinogenemia following substantial bleeding occurs due to hemodilution from volume replacement or consumption by clot formation. Fibrinogen supplementation is critical to restore normal clot formation following substantial hemorrhage. Fibrinogen concentrate, cryoprecipitate or plasma are typically used for fibrinogen replacement in hypofibrinogenemia. Currently, there are no approved fibrinogen products for the supplementation of fibrinogen in acquired fibrinogen deficiency.

FIBRYGA is a highly purified, plasma derived, lyophilized, human plasma fibrinogen concentrate. FIBRYGA is formulated without added albumin and the purification process used in its manufacture includes two separate virus inactivation/removal steps. During the manufacturing process of FIBRYGA. FIBRYGA was first approved in the United States in 2017 and is licensed for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

The sBLA contains data from the FIBRES study, demonstrating the effectiveness and safety of FIBRYGA in a prospective, multicenter, randomized, active-control, non-inferiority study comparing fibrinogen concentrate (FIBRYGA) with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients. The primary outcome measure was to demonstrate the total number of allogeneic blood product (ABP) units transfused in the two groups the first 24 hours after termination of cardiopulmonary bypass (CPB). A total of 372 patients in the FIBRYGA arm and 363 patients in the cryoprecipitate arm were enrolled in FIBRES. The interim analysis of 302 in the FIBRYGA group and the 302 in the cryoprecipitate group comprised the efficacy analysis population. The FIBRES study met its primary endpoint, demonstrating that FIBRYGA is non-inferior to cryoprecipitate based on the total number of ABPs administered during the first 24 hours after termination of CPB; the mean CBP was 17.0±17.7 versus 17.4±17.0, respectively. Fibrinogen levels increased from 1.7 ± 0.6 g/L to 2.5 ± 0.6 g/L in the FIBRYGA group and from 1.7 ± 0.6 g/L to 2.3 ± 0.6 g/L for the cryoprecipitate group, representing a mean increase of 0.9 ± 0.4 g/L in the FIBRYGA group and 0.7 ± 0.4 g/L in the cryoprecipitate group.

The safety analysis population consisted of the modified intent-to-treat (mITT) population (n=735) from the FIBRES study. 372 patients were randomized to the FIBRYGA arm, and 363 patients were randomized to the Cryoprecipitate arm. All clinical safety data were adjudicated by an Independent Data Safety Monitoring Committee (IDSMC). There was a total of 40 deaths (10.8%) in the FIBRYGA arm and 29 deaths (8%) in the Cryoprecipitate arm. The most common cause of death in both arms was cardiac disorders, which is expected due to the nature of the patients' past medical history and the type of cardiac surgery the patients had.

The most common causes of death from fatal treatment-emergent adverse events (TEAEs) which occurred up to 28 days after CPB end were cardiac (n=10), stroke (n=2), sepsis (n=2), and intestinal or mesenteric ischemia (n=2) in the FIBRYGA arm. Similarly, the most common causes of death from fatal TEAEs which occurred up to 28 days after CPB end were cerebrovascular accidents (n=6), sepsis (n=5), cardiac (n=5), and multi-organ failure (n=4). It is difficult to determine if FIBRYGA was the cause of death for the patients on the FIBRYGA arm due to the fact that many of these patients had a complicated medical history, which may have put them at risk for more serious complications from surgery and the type of surgery differed from patient to patient, with some surgeries having more risk than others.

The most common adverse reactions (>5%) observed in the FIBRYGA arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure. Similarly, the most common adverse reactions (>5%) observed in the Cryoprecipitate arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, renal failure, thrombocytopenia, and pneumonia.

The most substantial risk of treatment with fibrinogen concentrates are thrombotic events. Seven patients (2%) died from either suspected or confirmed thromboembolic events (TEEs) on the FIBRYGA arm and 10 patients (2.8%) died from suspected on confirmed TEEs on the Cryoprecipitate arm. Overall, 32 patients (8.6%) experienced a total of 37 TEEs in the FIBRYGA arm and 45 patients (12.1%) experienced a total of 50 TEEs in the Cryoprecipitate arm. The most common TEE that occurred in both arms was a cerebrovascular accident. The TEE events that occurred on the FIBRYGA arm may have been caused by FIBRYGA, however, it is difficult to determine due to patients' underlying risk factors for the development of a TEE, the risk of TEEs associated with CPB, the type of the cardiac surgery the patients' had, and the risk of thrombosis from other blood products used. The risk of TEEs is adequately addressed in the prescribing information (PI).

Overall, the Applicant has provided substantial evidence of effectiveness and safety based on a single, adequate, and well controlled clinical investigation providing evidence of clinical benefit. The overall benefit risk assessment is favorable, and the review team recommends traditional approval of FIBRYGA for the use of fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

**Table 1. Baseline Demographic Information**

| Category | Octafibrin N=372 | Cryoprecipitate N=363 | Total N=735 |
|---|---|---|---|
| Age (years) | - | - | - |
| Mean (SD) | 61.03 (15.32) | 61.30 (14.64) | 61.16 (14.98) |
| Median (range) | 65.00 (17-86) | 64.00 (18-88) | 64.00 (17-88) |
| Sex, n (%) | - | - | - |
| Female | 113 (30.38) | 105 (28.93) | 218 (29.66) |
| Male | 259 (69.62) | 258 (71.07) | 517 (70.34) |
| Race, n (%) | - | - | - |
| American Indian or Alaska Native | 1 (0.27) | 2 (0.55) | 3 (0.41) |
| Asian | 48 (12.90) | 54 (14.88) | 102 (13.88) |
| Black or African American | 3 (0.81) | 5 (1.38) | 8 (1.09) |
| White | 268 (72.04) | 253 (69.70) | 521 (70.88) |
| Other | 52 (13.98) | 49 (13.50) | 101 (13.74) |
| BMI ($kg/m^2$) | - | - | - |
| Mean (SD) | 22.77 (4.70) | 22.89 (4.40) | 22.83 (4.55) |
| Median (range) | 22.15 (13.23–52.63) | 22.80 (11.11–35.00) | 22.51 (11.11–52.63) |

Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 8

*Reviewer Comment:*

*There were no notable differences between the FIBRYGA group and the cryoprecipitate group with regard to age, gender, race, or body mass index (BMI).*

*Additionally, there were no notable differences between the FIBRYGA group and the cryoprecipitate group with regard to comorbidities which included, but were not limited to history of myocardial infarction, left ventricular ejection fraction, pulmonary hypertension, diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, dyslipidemia, and chronic lung disease. Additionally, there were no notable differences between the FIBRYGA group and the cryoprecipitate group with regard to comorbidities which included, but were not limited to history of myocardial infarction, left ventricular ejection fraction, pulmonary hypertension, diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, dyslipidemia, and chronic lung disease.*

1.2 Patient Experience Data

**Data Submitted in the Application**

| Check if Submitted | Type of Data | Section Where Discussed, if Applicable |
|---|---|---|
| ☐ | Patient-reported outcome | |
| ☐ | Observer-reported outcome | |
| ☐ | Clinician-reported outcome | |

| | | |
|---|---|---|
| ☐ | Performance outcome | |
| ☐ | Patient-focused drug development meeting summary | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) | |
| ☐ | Observational survey studies | |
| ☐ | Natural history studies | |
| ☐ | Patient preference studies | |
| ☐ | Other: (please specify) | |
| | **If no patient experience data were submitted by Applicant, indicate here.** | |
| **Check if Considered** | **Type of Data** | **Section Where Discussed, if Applicable** |
| ☐ | Perspectives shared at patient stakeholder meeting | |
| ☐ | Patient-focused drug development meeting | |
| ☐ | FDA Patient Listening Session | |
| ☐ | Other stakeholder meeting summary report | |
| ☐ | Observational survey studies | |
| ☐ | Other: (please specify) | |

## 2. CLINICAL AND REGULATORY BACKGROUND

FIBRYGA was originally approved on December 24, 2020, 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. See below Section 2.5 for a summary of pre- and post-submission regulatory activity related to the submission. See below Section 2.5 for a summary of pre- and post-submission regulatory activity related to the submission.

### 2.1 Disease or Health-Related Condition(s) Studied

Fibrinogen is a glycoprotein encoded by three different genes and is the major structural component of clots and the substrate for thrombin, plasmin, and factor XIIIa. It has a half-life of 3 to 4 days, and plasma concentrations in humans average 200 to 400 mg/dl.

Fibrinogen plays a critical role in hemostasis and facilitates wound healing. Disorders of fibrinogen can have both hemorrhagic and thrombotic manifestations and may also affect pregnancy. Disorders of fibrinogen can be acquired or inherited and can result in either a

quantitative or qualitative problem with fibrinogen. Both acquired and inherited hypofibrinogenemia can cause serious bleeding and an increase in prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time[1].

Acquired hypofibrinogenemia is an acquired disorder that results in reduced levels of circulating fibrinogen below normal values, typically >150mg/dL. Circulating fibrinogen usually must be >100mg/dL to prevent clinical bleeding. Common causes of hypofibrinogenemia include bleeding, liver disease, disseminative intravascular coagulation, hemophagocytic lymphohistiocytosis, or plasma exchange therapy. Treatment for acquired fibrinogenemia should include treating the underlying cause along with fibrinogen replacement. Hypofibrinogenemia following substantial bleeding occurs due to hemodilution from volume replacement or consumption by clot formation. Fibrinogen supplementation is critical to restore normal clot formation following substantial hemorrhage. Fibrinogen concentrate, cryoprecipitate or plasma are typically used for fibrinogen replacement in hypofibrinogenemia.

There are several potential products which may be used to treat acquired hypofibrinogenemia. Plasma is commonly used for severe hemorrhage after both trauma and surgery, although recent systematic reviews suggest that there is no benefit for the use of plasma in most clinical indications, including surgery, except for trauma[2]. Additionally, large volumes of plasma must be used for effective fibrinogen replacement and the concentrations of fibrinogen in plasma are not consistent and may range from 1 to 3 g/L[2]. Additionally, large volumes of plasma must be used for effective fibrinogen replacement and the concentrations of fibrinogen in plasma are not consistent and may range from 1 to 3 g/L[2]. Cryoprecipitate includes fibrinogen, as well as von Willebrand factor and Factor XIII and is widely used for fibrinogen replacement. Each unit of Cryoprecipitate contains about 200 to 250 mg of fibrinogen, with a standard dose of 8 to 10 units[2]. However, there are safety concerns with the use of cryoprecipitate as it comes from multiple donors and there is no antiviral processing[2]. Guidelines suggest the use of specific factor concentrations (if available) before the use of cryoprecipitate to control bleeding related to low fibrinogen levels[2]. The use of fibrinogen concentrates are currently approved for the treatment of acute bleeding episodes in adults and children with congenital fibrinogen deficiency, however, there are currently no fibrinogen concentrates approved for the treatment of acute bleeding episodes in acquired hypofibrinogenemia.

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

There are no approved products for acquired fibrinogen deficiency.

The following fibrinogen products are licensed for congenital fibrinogen deficiency:

- FIBRYGA – Octafibrin (Octapharma)
- RIASTAP (CSL Behring)

2.3 Safety and Efficacy of Pharmacologically Related Products

Given in adequate doses, both FFP and cryoprecipitate are effective in hypofibrinogenemia. Given the low fibrinogen concentration compared to fibrinogen concentrates, larger volumes of

1 Casini, A., Berube, C. (2024). Disorders of Fibrinogen. *UpToDate. Retrieved July 11, 2024, from "*Disorders of fibrinogen - UpToDate".

2 Levy, J., Goodnough, L. How I use fibrinogen replacement therapy in acquired bleeding. *Blood. (2015) 125(9): 1387-1393.*

FFP and cryoprecipitate are required. These products do not have viral inactivation steps, contain additional plasma proteins such as von Willebrand factor, fibronectin, and possible allergens. Additionally, the amount of fibrinogen in these products is variable and multiple units may be required for transfusion. FFP also carries a risk of transfusion-related acute lung injury.

RiaSTAP was evaluated in subjects with congenital afibrinogenemia in the non-bleeding state and were administered a single dose of 70mg/kg and the mean change in the maximum clot firmness (MCF) pre- and 1-hour post-infusion without a pre-specified study success for hypothesis testing. The results of the study demonstrated that the mean change in MCF values closely approximately levels expected from adding known amounts of fibrinogen to plasma in-vitro. Pharmacokinetic studies were evaluated in children and adults and provided data in support of efficacy. The prescribing information for RiaSTAP recommends targeting a level of 100mg/dL of fibrinogen until hemostasis is achieved. No adverse events were noted following the single administration at the flat dose in the study evaluating CF to support accelerated approval on this surrogate endpoint.

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

FIBRYGA is approved in Canada and the EMA for acquired fibrinogen deficiency. The approval was based on the results of the same study that was under review for this sBLA submission.

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

**Table 2. Summary of Pre- and Post-Submission Regulatory Activity Related to the Submission**

| Activity | Date | Description |
|---|---|---|
| Type C Meeting: Request Letter (STN 125612) | July 5, 2023 | Submission of Type C pre-supplemental BLA (sBLA) meeting request to discuss whether - based on the data from the large, investigator-led, Phase 3, multicenter, randomized, active-control FIBRES study of fibrinogen supplementation in cardiac surgery in Canada - FIBRYGA is approvable for the supplemental indication *fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency* (b) (4) |
| Type C Meeting: Meeting Confirmation (STN 125612/120) | July 25, 2023 | FDA Type C Meeting Confirmation for meeting ID # 15142, BLS 125612/120, scheduled for Sep 26, 2023 |
| Type C Meeting: Briefing Package (STN 125612/120) | August 2, 2023 | Submission of briefing documents for Type C meeting ID # 15142 scheduled for Sep 26, 2023. |
| Type C Meeting: Amended Briefing Package (STN 125612/120) | September 14, 2023 | Submission of modifications to sections 5, 12 and 13 of the Type C meeting package, as recommended by FDA in an informal meeting on Sep 13, 2023, including the following modified indication and question for discussion:<br>Does FDA agree that—based on the data from the large, investigator-led, Phase 3, multicenter, randomized, active-control FIBRES study of fibrinogen supplementation in cardiac surgery in Canada—FIBRYGA is approvable for *fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency*? |
| Type C Meeting: Preliminary Meeting Responses (STN 125612/120) | September 20, 2023 | As preliminary response FDA agrees to the above question for discussion and recommends as a next step that a supplement to the FIBRYGA BLA is submitted for review with the indication noted above. |

| **Activity** | **Date** | **Description** |
|---|---|---|
| Initial Pediatric Study Plan: Submission of agreed iPSP (pre-BLA STN 008748) | December 21, 2023 | Submission of the agreed iPSP for FIBRYGA for the indication *Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency*. |
| Initial Pediatric Study Plan: FDA Agreement (pre-BLA STN 008748) | January 19, 2024 | Submission of the agreed iPSP for FIBRYGA for the indication *Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency*. |
| cPAS - Efficacy Supplement: Submission (STN 125612/133) | January 30, 2024 | Submission of Efficacy Supplement to include *Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency as* additional indication for *FIBRYGA.*<br>The label extension application is based on the results of clinical study FIBRES (*prospective, multicenter, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients*). |
| cPAS - Efficacy Supplement: Acknowledgement Letter (STN 125612/133) | February 13, 2024 | FDA Acknowledgement Letter for STN 125612/133.<br>Reason for submission:<br>- To obtain FDA's approval of Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency and<br>- To obtain label extension based on the results from the FIBRES clinical study.<br>Target review goal date: July 31, 2024 (Priority Review). |
| cPAS - Efficacy Supplement: Filing Notification (STN 125612/133) | March 12, 2024 | FDA Filing Notification for STN 125612/133 confirming review classification (Priority) and review goal date (July 31, 2024). FDA acknowledged that PREA has been addressed for this supplement. |

Source: Adapted from sBLA 125612/133; Applicant's response to FDA's Information Request dated June 12, 2024
Abbreviations: iPSP, Initial Pediatric Study Plan; PREA, Pediatric Research Equity Act; sBLA, supplemental biologics license application; STN, submission tracking number

### 2.6 Other Relevant Background Information

N/A

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The BLA was submitted electronically and formatted as an electric Common Technical Document according to FDA guidance for electronic submission. This submission consisted of the five modules in the common technical document structure. It was adequately organized and integrated to conduct a complete clinical review.

### 3.2 Compliance With Good Clinical Practices And Submission Integrity

The Applicant noted that the study complied with good clinical practices. There was no clinical study conduct or data integrity issues that impacted the clinical review of this submission.

3.3 Financial Disclosures

| |
|---|
| **Covered clinical study** (name and/or number): FIBRES |
| Was a list of clinical investigators provided? X Yes ☐ No (Request list from applicant) |
| Total number of investigators identified: 11 |
| 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)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: _____<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in sponsor of covered study: _____<br>Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☐ No (Request details from applicant)<br>Is a description of the steps taken to minimize potential bias provided?<br>☐ Yes ☐ No (Request information from applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0<br>Is an attachment provided with the reason? ☐ Yes ☐ No (Request explanation from applicant) |

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

4.1 Chemistry, Manufacturing, and Controls

FIBRYGA is a highly purified, plasma-derived, lyophilized, human plasma fibrinogen concentrate. FIBRYGA is formulated without added albumin and the purification process used in its manufacture includes two separate virus inactivation/removal steps.

4.2 Assay Validation

N/A

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 with the original approval.

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

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

The pharmacokinetics (PK) of FIBRYGA has been assessed in previous submissions (Study FORMA-01 and Study-FORMA-04). The PK parameters after a single dose of 70 mg/kg is summarized in Table 3:

**Table 3. Pharmacokinetic Parameters for Fibrinogen Activity**

| Parameters | Adult and Adolescent Subjects (n=21) Mean ± SD (range) | Pediatric Subjects 6 to <12 years of age (n=8) Mean ± SD (range) | Pediatric Subjects <6 years of age (n=5) Mean ± SD (range) |
|---|---|---|---|
| Half-life [her] | 75.9 ± 23.8 (40.0-157.0) | 66.1 ± 12.1 (57.7-91.6) | 56.9 ± 10.8 (45.6-67.0) |
| Cam [mg/dL] | 139.0 ± 36.9 (83.0-216.0) | 112.4 ± 19.8 (93.0-154.0) | 99.0 ± 4.9 (94.0-106.0) |
| AUC [mg*he/mL] | 124.8 ± 34.6 (65.7-193.3) | 102.1 ± 22.2 (78.2-140.9) | 83.8 ± 12.4 (73.2-97.4) |
| AUCnorm for dose of 70 mg/kg [mg*hr/mL] | 113.7± 31.5 (59.7-175.5) | 97.2 ± 21.2 (74.4-134.2) | 79.8 ± 11.8 (69.7-92.8) |
| Incremental IVR mg/dL/(mg/kg) | 1.8 ± 0.5 (1.1-2.6) | 1.5 ± 0.3 (1.3-2.1) | 1.3 ± 0.1 (1.3-1.4) |
| Clearance [mL/hr/kg] | 0.7 ± 0.2 (0.4-1.2) | 0.7 ± 0.1 (0.5-0.9) | 0.9 ± 0.1 (0.8-1.0) |
| Mean residence time [hr] | 106.3 ± 30.9 (58.7-205.5) | 92.2 ± 17.1 (79.7-126.7) | 78.4 ± 14.0 (63.6-91.5) |
| Volume of distribution at steady state [mL/kg] | 70.2 ± 29.9 (36.9-149.1) | 67.2 ± 8.2 (52.8-76.8) | 68.6 ± 4.4 (63.9-72.7) |

Source: Study FORMA-01 Tables 10 and 14, Study FORMA-04 Table 28.
Abbreviations: $C_{max,}$ maximum plasma concentration; AUC, area under the curve; $AUC_{norm}$, area under the curve normalized to the dose administered; SD, standard deviation

In Study FIBRES, the effect of Octafibrin on plasma fibrinogen levels restoration was assessed by comparing fibrinogen levels (Clauss assay) within 75 minutes before and after the start of infusion of the first dose of Octafibrin and cryoprecipitate.

As shown in Table 4, in subjects with available plasma fibrinogen levels the first dose of *Octafibrin* (mean (±SD) dose: 53.98 (12.66) mg/kg) increased the plasma fibrinogen level from a mean (±SD) of 1.722 g/L (±0.646) to 2.454 g/L (±0.592). The first dose of cryoprecipitate

increased the plasma fibrinogen level from a mean (±SD) of 1.739 g/L (±0.583) to 2.322 g/L (±0.578).

**Table 4. Plasma Fibrinogen Level Before and After First Dose of IMP, Measured Using the Clauss Assay (mITT Population; N=735)**

| Variable | Octafibrin (g/L) | | | Cryoprecipitate (g/L) | | |
|---|---|---|---|---|---|---|
| | N | Mean (±SD) | Median (IQR) | N | Mean (±SD) | Median (IQR) |
| Pre-IMP | 223 | 1.722 (±0.646) | 1.60 (1.30-2.00) | 182 | 1.739 (±0.583) | 1.67 (1.34-2.00) |
| Post-IMP | 253 | 2.454 (±0.592) | 2.41 (2.12-2.79) | 242 | 2.322 (±0.578) | 2.23 (1.97-2.54) |

Source: Applicant. Study FIBRES report Table 16.
Only measurements taken within 75 minutes before and after start of the infusion are included in the analysis. N values represent the number of patients out of the mITT population (n=735) that have fibrinogen level data available.
Abbreviations: IMP, investigational medicinal product; IQR , interquartile range; mITT, modified intention-to-treat; SD, standard deviation.

In addition to plasma fibrinogen levels, FIBTEM A10 (fibrinogen function) values were measured within 75 minutes before and after the start of infusion of the first dose of Octafibrin or cryoprecipitate. Data from FIBTEM A10 were available in approximately 18% of patients in the Octafibrin group and 16% of patients in the cryoprecipitate group. Prior to the first dose of *Octafibrin*, the mean (±SD) FIBTEM A10 value in the mITT population was 8.675 mm (±3.097), with a median (IQR) of 8.00 mm (7.00–10.00). Values for the cryoprecipitate group were similar, with a mean (±SD) of 8.884 mm (±4.388) and median (IQR) of 8.00 mm (6.00–11.00). Following the first dose, the mean (±SD) FIBTEM A10 value increased to 14.345 mm (±4.029), with a median (IQR) of 15.00 mm (11.00–17.00). For the cryoprecipitate group, the mean (±SD) FIBTEM A10 value increased to 13.500 mm (±3.692), with a median (IQR) of 13.00 mm (11.00–16.00). (Table 5)

**Table 5. FIBTEM A10 Before and After First Dose of IMP (mITT Population; N=735)**

| Variable | Octafibrin (g/L) | | | Cryoprecipitate (g/L) | | |
|---|---|---|---|---|---|---|
| | N | Mean (±SD) | Median (IQR) | N | Mean (±SD) | Median (IQR) |
| Pre-IMP | 77 | 8.675 (±3.097) | 8.00 (7.00-10.00) | 69 | 8.884 (±4.388) | 8.00 (6.00-11.00) |
| Post-IMP | 55 | 14.345 (±4.029) | 15.00 (11.00-17.00) | 46 | 13.500 (±3.692) | 13.00 (11.00-16.00) |

Source: Applicant. Study FIBRES report Table 17.
Only measurements taken within 75 minutes before and after start of the infusion are included in the analysis. N values represent the number of patients out of the mITT population (n=735) that have fibrinogen level data available.
Abbreviations IMP, investigational medicinal product; IQR. interquartile range; mITT, modified intention-to-treat; SD, standard deviation.

*Reviewer's Comment:*

*The Clauss assay is a quantitative, clot-based, functional assay. FIBTEM assay is one of the thromboelastometry assay, which quantitatively measures the ability of whole blood to form a clot. The results of fibrinogen restoration from Clauss assay and FIBTEM A10 assay*

*were consistent. In both assays, infusion of the first dose of Octafibrin resulted in similar increase of fibrinogen activity levels, compared to cryoprecipitate.*

4.5 Statistical

The statistical reviewer has evaluated the Applicant's statistical findings, please refer to the statistical review memo for additional details. The applicant's calculations were reproducible.

4.6 Pharmacovigilance

The pharmacovigilance plan for FIBRYGA has both important potential risks and important identified risks, and for both the Applicant proposes routine pharmacovigilance. The pharmacovigilance reviewer did not identify additional risks, nor proposes additional pharmacovigilance is required routine pharmacovigilance is appropriate to monitor the populations previously listed. The proposed PVP is adequate to monitor post-marketing safety for FIBRYGA with routine pharmacovigilance in accordance with 21 CFR 600.80. OBPV/DPV has the following recommendations for post marketing safety monitoring of FBRYGA:

- Continue routine pharmacovigilance with adverse event reporting in accordance with 21 CFR 600.80
- The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a new safety-related post marketing requirement (PMR) study. There is no safety-related study as an agreed upon post marketing commitment (PMC) at this time.

An Independent Data Safety Monitoring Committee (IDSMC) was in place to review accumulating safety, endpoint, and other study data (recruitment, retention and compliance, data quality and timeliness, risk vs. benefit).

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

5.1 Review Strategy

This efficacy supplement reviewed focused on data from the study FIBRES, to evaluate FIBRYGA for the indication of fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency. Analyses were performed largely using (b) (4) (b) (4) based on the submitted data analysis datasets.

The draft PI was reviewed, followed by review of the final study report for the FIBRES study, responses to clinical information requests seeking clarification of information in the submission, and financial disclosure forms.

*Reviewer Comment:*

- *Dr. Kaushal reviewed the clinical efficacy portion of this original application. Dr. Johnson reviewed the clinical safety portion of this original application. Supervision was provided by Office managers.*

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

- FIBRYGA draft PI
- December 24, 2020, FIBRYGA approval letter
- Final Study report for the FIBRES study and FIBRES study data provided in the original submission
- Information and additional data submitted by the Applicant in response to information requests

The following materials from the submission were reviewed:

**Table 6. Materials Reviewed From Submission**

| Module | Information |
|---|---|
| 1.9 | Pediatric Administrative Information |
| 1.14 | Labeling |
| 2.5 | Clinical Overview |
| 2.7 | Clinical Summary |
| 2.7.3 | Summary of Clinical Efficacy |
| 2.7.4 | Summary of Clinical Safety |
| 5.2 | Tabular Listing of all Clinical Studies |
| 5.3.5 | Reports of Efficacy and Safety Studies |
| 5.3.5.1 | Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication |
| 5.4 | Literature References |

Source: FDA reviewer

5.3 Table of Studies/Clinical Trials

**Table 7. Studies/Clinical Trials**

| Study Name | Population, No. of Patients Enrolled (Age) | Design/Study Site/Location Study Period | Test Product(s)/Dosage Regimen/Duration of Treatment | Evaluation Criteria | Endpoints |
|---|---|---|---|---|---|
| FIBRES | Patients with acquired fibrinogen deficiency<br>N=735<br>(mITT population)<br>17–88 years | Pragmatic, prospective, multicenter, randomized, active-control, single-blinded, non-inferiority, Phase 3 study in bleeding adult cardiac surgical patients Multicenter:<br>11sites in Canada<br>23-Feb-2017 to 28-Nov-2018 | Octafibrin<br>Cryoprecipitate<br>Dosage Regimen:<br>Patients with suspected or confirmed acquired hypofibrinogenemia and hemorrhage after cardiac surgery were randomly assigned to receive 4 g of fibrinogen concentrate (Octafibrin, Octapharma AG) or 10 units of cryoprecipitate.<br><br>Duration:<br>Each patient participated in the trial for 28 days (during which safety outcomes were measured). | Efficacy assessed by cumulative ABP units administered after CPB, major bleeding after CPB, and posttreatment change in fibrinogen concentration<br>Safety outcomes assessed over 28 days | Primary Endpoint:<br>-Total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the first 24 hours after termination of CPB<br>Safety Endpoints:<br>AEs, SAEs, mortality, laboratory data |
| FORMA-01 | Patients with congenital fibrinogen deficiency<br>N=22<br>≥12 years<br>(12–53 years) | Multinational, multicenter, prospective, randomized, controlled, crossover, Phase 2 study<br>Multicenter: 10 centers in India, Switzerland, Iran, UK, USA, and Bulgaria<br>04-Jun-2013 to 19-Jan-2015 | *Octafibrin* and comparator Haemocomplettan® P/RiaSTAP™<br>Single administration of 70 mg/kg<br>Duration:<br>Two periods of 45 days each | PK<br>Efficacy*<br>Safety | Primary Endpoint:<br>- PK: AUC (fibrinogen) versus Haemocomplettan® P/RiaSTAP™<br>- Efficacy: MCF at 1-hour post infusion versus Haemocomplettan® P/RiaSTAP™<br>- Safety: AEs, vital signs, laboratory safety |
| FORMA-02 | Patients with congenital fibrinogen deficiency<br>Interim analysis:<br>FAS-Bleeding | Prospective, open-label, uncontrolled, Phase 3 study<br>Multicenter | Octafibrin<br>Treatment of BEs:<br>Doses specific to minor bleeding, major bleeding, minor surgeries, and major surgeries | Efficacy<br>Safety<br>IVR | Primary Endpoint:<br>- Efficacy in treating the first documented BE of each patient |

| Study Name | Population, No. of Patients Enrolled (Age) | Design/Study Site/Location Study Period | Test Product(s)/Dosage Regimen/Duration of Treatment | Evaluation Criteria | Endpoints |
|---|---|---|---|---|---|
| | N=11<br>13–53 years<br>Surgical Prophylaxis<br>N=4<br>19−42 years<br>Final analysis:<br>FAS-Bleeding<br>N=24<br>12–54 years<br>Surgical Prophylaxis<br>N=9<br>12−49 years | 13-Oct-2015 to14-Feb-2018<br>Interim analysis:<br>25-Mar-2016 | Duration:<br>Individual treatment observation period lasted ≥3 days for minor and ≥7 days for major Bes<br>Individual patient observation<br>Surgical observation period started with the first dose of Octafibrin administered prior to Day 1 and lasted ≥3 days for minor and ≥7 days for major surgeries or until the day of the last postoperative infusion, whichever came last | | - Safety and tolerability (AEs, vital signs, laboratory safety, immunogenicity) |
| FORMA-04 | Pediatric patients <12 years of age with congenital fibrinogen deficiency<br>firstBLEED/first BLEED-PP:<br>N=8<br>3.0–10.0 years<br>BLEED/BLEEDPP:<br>N=8<br>3.0–10.0 years<br>PK/PK-PP:<br>N-13<br>1.0–10.0 years<br>SURG/SURGPP:<br>N=3<br>1.0–5.0 years | Prospective, open-label, uncontrolled, Phase 3 study<br>Multicenter:<br>15-Dec-2015 to 11-Jun-2019 | Octafibrin<br>Treatment of BEs:<br>Doses were specific to minor bleeding, major bleeding, minor surgeries, major surgeries and for PK studies.<br>Duration:<br>Individual treatment observation period lasted ≥3 days for minor and ≥7 days for major Bes<br>Surgical observation period started with the first dose of Octafibrin administered prior to surgery (Day 1) and lasted ≥3 postoperative days for minor and ≥7 postoperative days for major surgeries or until the day of the last postoperative infusion,<br>whichever came last | Efficacy<br>Safety<br>PK | Primary Endpoint:<br>- Efficacy in treating the first documented BE of each patient<br>- Safety and tolerability (AEs, vital signs, laboratory safety) |
| FORMA-07<br>*Ongoing* | Patients with congenital fibrinogen deficiency | Post-marketing, observational, Phase 4 study | *Octafibrin* dosing as per the locally approved<br>package insert: | Safety Efficacy | Primary Endpoint: |

| Study Name | Population, No. of Patients Enrolled (Age) | Design/Study Site/Location Study Period | Test Product(s)/Dosage Regimen/Duration of Treatment | Evaluation Criteria | Endpoints |
|---|---|---|---|---|---|
| | Any age | Centers: all sites that intend to treat patients with *Octafibrin* after marketing authorization has been granted and the product is commercialized<br>Q4 2020 to Q4 2027 | North America: dosing to achieve a recommended target fibrinogen plasma level of 100 mg/dL for minor bleeding and 150mg/dL for major bleeding<br>Europe: dosing to achieve a target fibrinogen plasma level of 100 mg/dL, maintained until hemostasis is secured | | - Incidence of thromboembolic ADRs in patients receiving *Octafibrin* for on-demand treatment of BEs (with special focus on major BEs)<br>- Safety (ADRs, SADRs, and ADRs of special interest, including thromboembolic events) |

Source: Adapted from sBLA 125612/133; Section 5.2 of Submission, Tabular Listing of All Clinical Studies, pages 1-9/9

Abbreviations: ABP, allogeneic blood product; ADR, adverse drug reaction; AEs, adverse events; AUC, area under the concentration-time curve; BE, bleeding episode; CI, confidence interval; Cmax, maximum plasma concentration; CPB, cardiopulmonary bypass; FAS, full analysis set; IVR, in vivo recovery; mITT, modified intent-to-treat; MCF, maximum clot firmness; PK, pharmacokinetics; RBC, red blood cell; SADR, serious adverse drug reaction; Tmax, time to maximum concentration; UDPB, Universal Definition of Perioperative Bleeding; VSs, steady-state volume of distribution

5.4 Consultations

No internal FDA consultants were requested by the clinical team during the review of this sBLA.

5.4.1 Advisory Committee Meeting (if applicable)

Not Applicable; An advisory committee meeting was not convened because the biologic is not the first in its class. Additionally, the review of the application did not raise significant safety or efficacy concerns that would warrant a public discussion and could not be addressed through information in the label. Consultative expertise was not required, and no public health concerns arose upon review of this file.

5.4.2 External Consults/Collaborations

There were no external consults or collaborations that were requested by the clinical reviewer in the review of this BLA.

5.5 Literature Reviewed (if applicable)

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

FIBrinogen Replenishment in Surgery (FIBRES), initially also referred to as FORMA-06 is a prospective, multicenter, randomized, active-control, non-inferiority study comparing fibrinogen concentrate with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac surgical patients.

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to demonstrate that the fibrinogen concentrate *Octafibrin* is non-inferior to cryoprecipitate in terms of efficacy in bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standard.

Exploratory secondary objectives included:

- Comparison of efficacy as measured by the total and individual number of units of ABPs transfused from the beginning of surgery up to postoperative day 7
- Comparison of bleeding during the first 24 hours after termination of CPB
- Comparison of the effect on fibrinogen levels observed within one hour before and one hour after fibrinogen supplementation
- Comparison of safety as measured by adverse events (AEs) and SAEs during the first 28 days after termination of CPB

Comparison of other secondary safety endpoints, including duration of mechanical ventilation, duration of intensive care unit (ICU) stay, and duration of hospitalization.

6.1.2 Design Overview

This was a prospective, multicenter, randomized, active-control, single-blinded, non-inferiority Phase 3 trial in adult cardiac surgical patients.

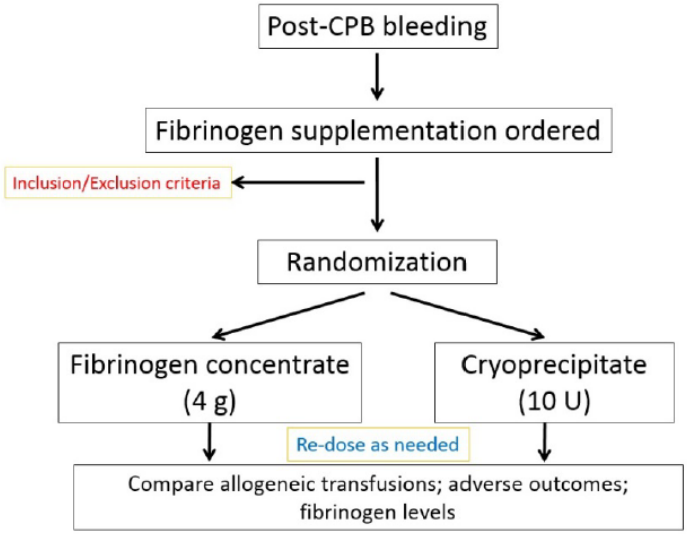
Patients were randomized to receive equivalent doses of fibrinogen content, of either fibrinogen concentrate (*Octafibrin*) or cryoprecipitate when the blood bank received the first order for

fibrinogen supplementation and deemed it to be in accordance with accepted clinical standards. Patients were treated according to their assigned group each time fibrinogen supplementation was ordered during the treatment period (24 hours after termination of CPB).

*Reviewer Comment:*

- *As above in regulatory history, there was no agreement made on the primary or secondary endpoints as this study was not conducted under IND. At the pre-BLA meeting, this endpoint was reasonable to support the claim of supplementation of fibrinogen for acquired hypofibrinogenemia.*
- *This trial did not include a placebo arm, as delaying supplementation in bleeding patients would withhold treatment to expose patients to blood loss.*

**Figure 1. Study Design**




Source: Adapted from sBLA 125613/133; Clinical Study Report, Figure 1 Study Design page 30/4585
Abbreviations: CPB, cardiopulmonary bypass

### 6.1.3 Population

The FIBRES patient population mirrored inclusion and exclusion criteria. This study was conducted in patients ≥ 18 years of age. Patients undergoing cardiac surgery with CPB in whom fibrinogen supplementation was ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia)

The most common surgical procedures in both groups were Aortocoronary bypass (ACB) and aortic valve repair or replacement.

### 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 the local regulations in vials containing 1g of lyophilized fibrinogen concentrate powder for reconstitution with 50 mL of water for injection (WFI). Patients randomized to the FIBRYGA arm will receive 4g each time fibrinogen supplementation is ordered during the first 24 hours after termination of CPB.

*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, FIBRYGA.*

6.1.5 Directions for Use

Each time fibrinogen supplementation was ordered, patients received either cryoprecipitate (1 dose =10 units = approximately 4 g) or purified fibrinogen concentrate (1 dose =4 g) infused in 10 minutes according to their group assignment.

Clinicians may opt to switch from one therapy to the other during the treatment period. The reasons for these requests were to be collected and described.

The amount of fibrinogen in each unit of cryoprecipitate was estimated to be approximately 400 mg. Thus, 4 g of fibrinogen concentrate was considered dose-equivalent to 10 units of cryoprecipitate. This is the recommended dose for fibrinogen supplementation in the setting of acute bleeding.

FIBRYGA or cryoprecipitate was administered by intravenous injection using an established intravenous route in bleeding patients developing acquired fibrinogen deficiency during cardiac surgery. FIBRYGA was prepared in accordance with investigational medicinal product (IMP) instructions and was administered after reconstitution. Cryoprecipitate was provided by the local blood bank and was administered after thawing.

6.1.6 Sites and Centers

Eleven Canadian hospitals participated.

6.1.7 Surveillance/Monitoring

An IDSMC reviewed accumulating safety, endpoint, and other study data (recruitment, retention, and compliance, data quality and timeliness, risk versus benefit). The function of the IDSMC was to protect and serve the recruited patients, particularly pertaining to patient safety, as well as to assist and advise the Sponsor on medical questions and issues of study conduct and continuation. The IDSMC was independent of the investigating team and the Sponsor in operating and formulating recommendations.

6.1.8 Endpoints and Criteria for Study Success

The primary efficacy endpoint was the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the 24 hours after termination of CPB.

Secondary endpoints included:

Number of units of ABPs administered up to 7 days after surgery start.

Major bleeding after the index surgery based on the Universal Definition of Perioperative Bleeding (UDPB) in cardiac surgery was a secondary outcome.

**Figure 2. Bleeding Categories According to the Universal Definition of Perioperative Bleeding in Cardiac Surgery**

| Bleeding definition | Postoperative chest tube blood loss within 12 h (mL) | RBC (units) | FFP (units) | PLT (units) | PCC | rFVIIa | Re-exploration /tamponade |
|---|---|---|---|---|---|---|---|
| Class 0 (insignificant) | <600 | 0 | 0 | 0 | No | No | No |
| Class 1 (mild) | 601–800 | 1 | 0 | 0 | No | No | No |
| Class 2 (moderate) | 801–1000 | 2–4 | 2–4 | Yes | Yes | No | No |
| Class 3 (severe) | 1001–2000 | 5–10 | 5–10 | NA | NA | No | Yes |
| Class 4 (massive) | >2000 | >10 | >10 | NA | NA | Yes | NA |

Source: Adapted from sBLA 125612/133 CSR
If different categories indicate mixed definitions of bleeding, the worst definition applies [60].
Abbreviations: FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PLT, platelets (pooled or apheresis; RBC, red blood cell; rFVIIa, recombinant activated factor VII

UDPB is defined as nine different clinical endpoints, including chest tube output, delay in sternal closure, re-exploration/tamponade and use of allogeneic blood and factor products. Based on these components, UDPB defines bleeding five peri-operative bleeding classes: insignificant, mild, moderate, severe, or massive. The UDPB was analyzed in a series of 1144 adult patients who underwent cardiac operations at a single institution. The nine event categories were successful in adjudicating patients to the appropriate UDPB class of bleeding. Additionally, the higher UDPB classification correlated with higher mortality in a univariate analysis.

*Reviewer Comment:*

- *In the FIBRES study, ABPs units were collected from the beginning of surgery until 7 days after surgery or until discharge, if earlier. Other hemostatic agents including DDAVP, PCC, rFVIIa, idaricizumab, and andexanet alfa were also included and captured.*

6.1.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis was performed on the modified intention-to-treat (mITT) population. The evaluation of the primary efficacy endpoint was additionally performed for the per-protocol population. The mITT population included all randomized patients who received at least one dose of IMP.

The per-protocol population consisted of all patients in the mITT population, excluding patients with major protocol deviations. The following patients were excluded:

- Patients who received an IMP different to the IMP assigned by randomization
- Patients who received less than 80% of the planned dose
- Patients who significantly violated the inclusion/exclusion criteria
- Patients with missing primary efficacy assessment

Approximately 1,200 bleeding adult cardiac surgical patients who required fibrinogen supplementation due to acquired hypofibrinogenemia after CPB were to be included; however, the study was terminated after an interim analysis.

The NI margin was 1.20 for the ratio of ABPs between the Octafibrin and the cryoprecipitate groups.

*Reviewer Comment:*

*It was not possible to blind investigators as the products have physical differences. Attempts were made to blind the clinicians outside of the OR and ICU per the clinical study report. However, it is unclear if this was successful.*

6.1.10 Study Population and Disposition

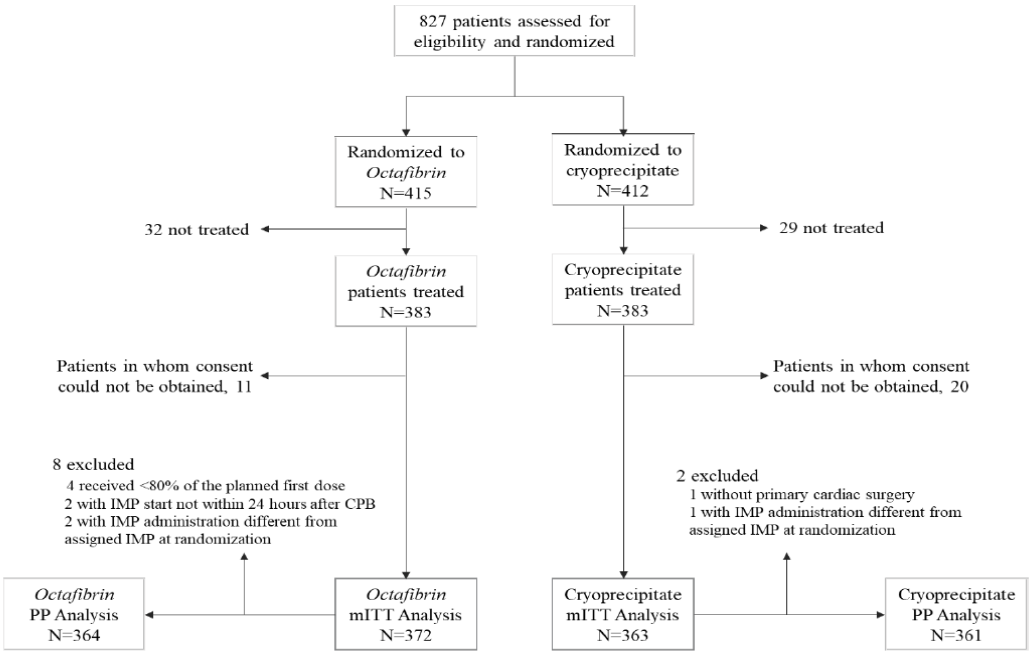
A total of 827 patients were assessed for eligibility and were randomized to receive Octafibrin or cryoprecipitate and were the miTT population. Of these, 32 patients in the *Octafibrin* group and 29 patients in the cryoprecipitate group did not receive treatment with the IMP. For 11 patients in the *Octafibrin* group and 20 patients in the cryoprecipitate group, consent was not obtained, so they were excluded from the mITT population. At the time of interim analysis, 688 patients were enrolled and were randomized to receive Octafibrin (N=342) or cryoprecipitate (N=346). For 11 patients in the *Octafibrin* group and 20 patients in the cryoprecipitate group, consent was not obtained, so they were excluded from the mITT population.
At the time of interim analysis, 688 patients were enrolled and were randomized to receive Octafibrin (N=342) or cryoprecipitate (N=346). Of these, 27 patients in the Octafibrin group and 22 patients in the cryoprecipitate group did not receive treatment with the IMP. For 13 patients in the Octafibrin group and 21 patients in the cryoprecipitate group, consent was not obtained, so they were excluded from the interim mITT population.

The interim mITT population, which was the primary analysis population, included 302 patients in the Octafibrin group and 303 patients in the cryoprecipitate group.

*Reviewer Comment:*

*Although the study population included the updated mITT and updated PP patients (see Figure 2 below), the interim mITT population was used for the primary endpoint as the study was stopped early based on the recommendation of the IDSMC for meeting the criterion for non-inferiority and therefore this population that was included in the label. The analysis for the primary efficacy endpoint in this memo includes both the Interim mITT and updated mITT.*

**Figure 3. Total Study Population and Disposition**




Source: sBLA 126612/133; Clinical Study Report page 51/4585
Abbreviations: CPB, cardiopulmonary bypass; PP, per-protocol

*6.1.10.1 Populations Enrolled/Analyzed*

**Inclusion Criteria:**

Patients undergoing cardiac surgery with CPB in whom fibrinogen supplementation was ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia).

**Exclusion Criteria**

1. Receipt of fibrinogen-containing products, including concentrate or cryoprecipitate, within 24 hours before surgery (to exclude patients with significant blood loss before surgery)
2. History of severe allergic reaction to cryoprecipitate or fibrinogen concentrate
3. Refusal of fibrinogen concentrate or cryoprecipitate due to religious or other reasons
4. Fibrinogen level known to be >3.0 g/L within 30 minutes of IMP order (to eliminate the risk of raising patients' fibrinogen levels to >4.0 g/L with supplementation, which is the upper limit of the normal range)
5. Known pregnancy

*Reviewer Comment:*

*Although patients with fibrinogen rich products within 24 hours prior to surgery were excluded, this did not include plasma. Patients undergoing plasmapheresis could be included.*

*6.1.10.1.2 Demographics*

**Table 8. Demographics**

| Category | Octafibrin N=372 | Cryoprecipitate N=363 | Total N=735 |
|---|---|---|---|
| Age (years) | - | - | - |
| Mean (SD) | 61.03 (15.32) | 61.30 (14.64) | 61.16 (14.98) |
| Median (range) | 65.00 (17-86) | 64.00 (18-88) | 64.00 (17-88) |
| Sex, n (%) | - | - | - |
| Female | 113 (30.38) | 105 (28.93) | 218 (29.66) |
| Male | 259 (69.62) | 258 (71.07) | 517 (70.34) |
| Race, n (%) | - | - | - |
| American Indian or Alaska Native | 1 (0.27) | 2 (0.55) | 3 (0.41) |
| Asian | 48 (12.90) | 54 (14.88) | 102 (13.88) |
| Black or African American | 3 (0.81) | 5 (1.38) | 8 (1.09) |
| White | 268 (72.04) | 253 (69.70) | 521 (70.88) |
| Other | 52 (13.98) | 49 (13.50) | 101 (13.74) |
| BMI ($kg/m^2$) | - | - | - |
| Mean (SD) | 22.77 (4.70) | 22.89 (4.40) | 22.83 (4.55) |
| Median (range) | 22.15 (13.23–52.63) | 22.80 (11.11–35.00) | 22.51 (11.11–52.63) |

Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 8
Abbreviations: BMI, body mass index; kg, kilogram; Max, maximum; Min, minimum; SD, standard deviation

Overall, the mean (± standard deviation [SD]) age of the mITT population was 61.2 years (±15.0), with a median (range) of 64.0 years (17–88). 29.7% of patients were female. A total of 70.9% were classed as White race, 13.9% as Asian, 1.1% as Black or African American, 0.4% as American Indian or Alaska Native and 13.7% as Other.

*Reviewer Comment:*

*There were no notable differences between the FIBRYGA group and the cryoprecipitate group with regard to age, gender, race, or body mass index (BMI).*

*6.1.10.1.3 Medical/Behavioral Characterization of the Enrolled Population*

All subjects had acquired hypofibrinogenemia. A total of 62.1% of the FIBRYGA group and 64.7% of the cryoprecipitate group had elective surgery. 71.8% of the FIRBYGA group and 71.6% of the cryoprecipitate group had surgery that was classified as complex. 16.9% of the FIBRYGA group and 10.5% of the cryoprecipitate group were classified as being in a critical state prior to surgery and were therefore considered high risk.

Additionally, there were no notable differences between the FIBRYGA group and the cryoprecipitate group with regard to comorbidities which included, but were not limited to history of myocardial infarction, left ventricular ejection fraction, pulmonary hypertension, diabetes mellitus, congestive heart failure, hypertension, peripheral vascular disease, dyslipidemia, and chronic lung disease.

*6.1.10.1.4 Subject Disposition*

See above Section 6.1.10 for details of subject disposition and below Section 6.1.12.7 for a table of the discontinuations from the study.

6.1.11 Efficacy Analyses

The primary analysis population was the mITT population. The primary endpoint for the study was comparison of the total number of ABPs administered to patients in the first 24 hours after termination of CPB. Efficacy data was collected up to 7 days after the start of surgery.

*6.1.11.1 Analyses of Primary Endpoint(s)*

The fibrinogen level increased from 1.7 ± 0.6 g/L to 2.5 ± 0.6 g/L in the FIBRYGA group and from 1.7 ± 0.6 g/L to 2.3 ± 0.6 g/L for the cryoprecipitate group, representing a mean increase of 0.9 ± 0.4 g/L in the FIBRYGA group and 0.7 ± 0.4 g/L in the cryoprecipitate group.

*Reviewer Comment:*

- *There was restoration of fibrinogen post infusion and provides "supplementation" of fibrinogen in acquired deficiency. Acquired deficiency differs from congenital deficiency where there is only an absence of fibrinogen. In acquired deficiency, there is not only a deficiency in fibrinogen, there is massive blood loss and depletion of other components in the coagulation system. Repleting fibrinogen provides supplementation of the level and along with other measures and hemostatic agents improves hemostasis.*
- *The expectation that the replenishment of solely fibrinogen will correct hemostasis is false.*

In the interim mITT population, the mean total number of ABPs administered during the first 24 hours after termination of CPB was 17.0±17.7 in the FIBRYGA arm versus 17.4±17.0 in the cryoprecipitate arm

In the mITT population, the mean total number of ABPs administered during the first 24 hours after termination of CPB was 16.3 ±16.7 in the FIBRYGA arm versus 17.0±16.1 in the cryoprecipitate arm.

From the start of surgery to 7 days later, in the mITT population, the mean (±SD) number of units of ABPs administered to patients in the *Octafibrin* group was 22.5 (±24.4). The mean (±SD) number of units of ABPs administered to patients in the cryoprecipitate group was 22.3 units (±21.7).

FIBRYGA was demonstrated to be non-inferior to cryoprecipitate based on the total number of units of allogeneic blood products (ABPs) administered during the first 24 hours after termination of cardiopulmonary bypass (CPB).

*Reviewer Comment:*

- *Based on both the mITT population and the interim mITT population, FIBRYGA demonstrated non-inferiority to cryoprecipitate based on the ordinary poisson regression, the 99.7% upper CI limit was 1.94 below the pre-specified 1.20 non inferiority margin using the pre specified alpha level of 0.00258. As this study was not conducted under IND, it is notable to point out that there was no agreement on these criteria prior to this review.*

*6.1.11.2 Secondary Endpoints*

Major bleeding was assessed using the UDPB in cardiac surgery during the first 24 hours after termination of CPB and the comparison of the effect on fibrinogen levels measured by the change in plasma fibrinogen concentration (as measured using the Clauss assay) before and after the first dose of fibrinogen supplementation.

**Figure 4. Distribution of Bleeding Categorized According to the UDPB during the first 24 hours (mITT population).**

| | Treatment Group | | |
|---|---|---|---|
| | ***Octafibrin*** | **Cryoprecipitate** | **Total** |
| | **N (%)** | **N (%)** | **N (%)** |
| Class 0 (insignificant) | 23 (6.18) | 16 (4.41) | 39 (5.31) |
| Class 1 (mild) | 11 (2.96) | 7 (1.93) | 18 (2.45) |
| Class 2 (moderate) | 162 (43.55) | 171 (47.11) | 333 (45.31) |
| Class 3 (severe) | 106 (28.49) | 115 (31.68) | 221 (30.07) |
| Class 4 (massive) | 69 (18.55) | 54 (14.88) | 123 (16.73) |
| N/A* | 1 (0.27) | 0 (0.00) | 1 (0.14) |
| Total | 372 (100.00) | 363 (100.00) | 735 (100.00) |

Source : sBLA 125612/133; CSR Table 15, page 65/4585
*One patient (b) (6) in the Octafibrin group died during surgery; bleeding was not categorized for this patient.
Abbreviations: CPB, cardiopulmonary bypass; mITT, modified intention-to-treat; N/A, not available; UDPB, universal definition of perioperative bleeding

*Reviewer Comment:*

> *Although the UDPB outcome measure was a secondary endpoint, it has been used with modifications in this study where 2 components were not used 1) sternal closure delay and 2) the use of cryoprecipitate. The UDPB utilizes 9 components for successful adjudication of patients to the appropriate UDPB class of bleeding, which was based on the original study and consensus opinion. Therefore, modifications and exclusion of some measures will not provide an accurate adjudication as done with the original scoring system. Thus, there is uncertainty in the score and utility with exclusion of these components.*

*6.1.11.3 Subpopulation Analyses*

The following is a summary of the pediatric data from the congenital fibrinogen deficiency study that is the basis of extrapolation from the adult to pediatrics.

Pediatric Data

Pediatric data used to support the use of FIBRYGA in children is being extrapolated from 3 additional completed studies that enrolled pediatric subjects, however, each of these studies had a different indication (congenital fibrinogen deficiency) from the pivotal adult trial's indication (acquired fibrinogen deficiency) being used to support this BLA.

Extrapolated Proposed Pediatric Dosing for Acquired Fibrinogen Deficiency: In the FIBRES study, patients on the Octafibrin arm received 4g of FIBRYGA which is equated to 50mg/kg of body weight in the final analysis of the study data. The proposed dosing for pediatric patients with acquired fibrinogen deficiency is extrapolated from data in adult patients in the FIBRES study and from studies in children with congenital fibrinogen deficiency, based on IVR. The extrapolation of this dose to patients younger than 12 years of age, taking into consideration the IVR of 1.4 mg/dL mg/kg body weight from pediatric patients with congenital fibrinogen deficiency, results in a dose of approximately 70 mg/kg body weight *Octafibrin*. Thus, a dose of 70 mg/kg is recommended for patients less than 12 years of age.

The three completed pediatric studies used were FORMA-04, FORMA-02 and FORMA-01. FORMA-04 enrolled 14 children aged 1 to 10 years with congenital fibrinogen deficiency. Six patients aged 12 to <18 years were also enrolled in study FORMA-01 and six were enrolled in the FORMA-02 study.

FORMA-04 is a prospective, open-label, uncontrolled Phase 3 trial study to assess the efficacy, safety, and pharmacokinetics of FIBRYGA for on-demand treatment of acute bleeding to prevent bleeding during and after surgery in pediatric subjects < 12 years of age with congenital fibrinogen deficiency. The primary endpoint of FORMA-04 was to evaluate the hemostatic efficacy of FIRBYGA for the first bleeding event for each patient. FIBRYGA was individually dosed to achieve a recommended target fibrinogen plasma level dependent on the type of bleeding or surgery (minor or major).

The dose was calculated individually as follows:

Fibrinogen dose (mg/kg body weight) = [Target peak plasma level (mg/dL) - measured level (mg/dL)**]/Median response* (mg/dL per mg/kg body weight) *

Eight patients were treated for a total of 10 BEs during the study, of which eight (80.0%) were minor and two (20.0%) were major. Treatment was considered successful for 100.0% (95% CI, 69.15–100.00) of the 10 BEs as adjudicated by the IDMEAC, with eight (80.0%) rated as excellent and two (20.0%) as good. The mean (±SD) first dose of FIBRYGA administered for the treatment of the first BE in each patient (N=8) was 71.7 mg/kg (±17.19). The median (range) first dose was 73.9 mg/kg (47.5–98.4). The mean (±SD) fibrinogen level at 1-hour post-infusion (N=8) was 98.9 mg/dL (±13.56), with a median (range) of 100.0 mg/dL (79.0–118.0). The efficacy of FIBRYGA for surgical prophylaxis was assessed in three surgical procedures in three patients, with two surgeries classed as minor and one as major.

The overall success rate of FIBRYGA for surgical prophylaxis was 100% (90% CI, 29.24, 100.00), with overall efficacy rated as excellent for all three (100.0%). There was one SAE classified as possibly related to treatment (portal vein thrombosis following splenectomy), with no deaths and no severe or serious allergic reactions observed during the study.

FORMA-02 is a prospective, open-label, uncontrolled, Phase 3 study to assess the efficacy and safety of FIBRYGA for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency. The primary endpoint of

** 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

* The median response in this dose calculation formula is the median incremental in vivo recovery reported in the final analysis of study FORMA-01

FORMA-02 was the hemostatic efficacy of FIRBYGA for the first bleeding event for each patient. *Octafibrin* was recommended to be individually dosed to achieve a target fibrinogen plasma level dependent on the bleeding type (minor or major) or type of surgery (minor or major). The target fibrinogen plasma levels were defined as follows:

- *Minor bleeding/minor surgery:* 100 mg/dL, with an accepted lower limit of 80 mg/dL
- *Major bleeding/major surgery:* 150 mg/dL, with an accepted lower limit of 130 mg/dL

Of the total patients treated for bleeding events (Bes) (n=89 episodes in 24 patients) or surgical prophylaxis (n=12 surgeries in nine patients), eight are included in both analyses as they received treatment for bleeding and surgical procedures. The Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC) rated treatment with FIBRYGA as successful in 88 (98.9%) Bes (90% CI, 0.954, 0.999), with treatment rated as excellent for 81 (91.0%), good for 7 (7.9%), and moderate for 1 (1.1%), the latter classed as a treatment failure. The mean (±SD) first dose of FIBRYGA administered for the treatment of the first BE in each patient (N=24) was 64.70 mg/kg (±15.23). The median (range) first dose was 66.37 mg/kg (33.90–102.60). After administration of these doses of FIBRYGA for the first BE, the mean (±SD) fibrinogen level at 1-hour post-infusion was 111.75 mg/dL (±28.74), with a median (range) of 109.00 mg/dL (43.00–204.00). At 3 hours post-infusion, the mean was 104.42 mg/dL (±29.53) and the median was 101.50 mg/dL (36.00– 199.00). The efficacy of FIBRYGA for surgical prophylaxis was assessed in 12 surgical procedures in nine patients, with 11 surgeries classed as minor and one as major. The overall success rate for FIBRYGA in surgical prophylaxis was 100% (90% CI, 0.816, 1.000). Overall efficacy was rated as excellent for the 11 minor surgeries (91.7%) and good for the one major surgery (8.3%).

FORMA-01 is a prospective, controlled, randomized, crossover study investigating the pharmacokinetic properties surrogate efficacy and safety of FIBRYGA compared to Haemocomplettan® P/RiaSTAPTM in patients with congenital fibrinogen deficiency 12 years of age and older. The primary endpoint of FORMA-01 was Comparison of AUCnorm between FIBRYGA and Haemocomplettan® P/RiaSTAP™; Comparison of MCF between FIBRYGA and Haemocomplettan® P/RiaSTAP™. Patients were administered a dose of 70mg/kg of FIBRYGA. Only safety was evaluated in this study and not efficacy.

Summary of Pediatric Safety Data

Safety data are available in 23 pediatric patients with congenital fibrinogen deficiency from the FORMA-01, FORMA-02, and FORMA-04 studies. Safety data for FIBRYGA for the treatment of congenital fibrinogen deficiency are available for one child aged 0 to 2 years (FORMA-04), five children aged 2 to 5 years (FORMA-04), eight children aged 6 to 12 years (FORMA-04), and nine children aged 12 to 16 years (FORMA-01 and FORMA-02). Safety was monitored by recording AEs, including allergic and hypersensitivity reactions, during the studies and measuring laboratory values, vital signs, physical examination, thrombogenicity (prothrombin fragment 1 and 2 [F1+F2] and D-dimers), viral safety (FORMA-01), and immunogenicity (FORMA-02).

FORMA-04

Children ages 0-2 years- A single patient aged 1 year (b) (6) received FIBRYGA in FORMA-04. No AEs were reported for this patient and thrombogenicity measurements were not available.

Children ages 2-5 years- Of the five children in this age group, two (patients (b) (6) and (b) (6)) experienced AEs. These included four TEAEs that occurred in patient (b) (6) and two non-

TEAEs that occurred in patient (b) (6) Patient (b) (6) experienced 2 non-TEAEs of hemarthrosis and tonsillitis which were considered to be unrelated to FIRBYGA. Patient (b) (6) experienced 4 AEs, including abdominal pain and procedural pain which were considered to be unrelated to FIBRYGA. This patient also experienced pyrexia and portal vein thrombosis, which were both considered to be possibly related to FIBRYGA.

Children ages 6 to 12 years- Of the eight children in this age group, 2 patients experienced AEs- including 3 TEAEs- all ecchymosis and one non-TEAE of an influenza-like illness. All of these AEs were considered to be unrelated to FIBRYGA.

FORMA-01 and FORMA-02

Adolescents ages 12 to 16 years- Of the nine children in this age range -2 children experienced AEs (1 patients with nasopharyngitis and pyrexia and a second patient with asthenia and decreased appetite) in FORMA-02. None of these AEs were considered related to FIBRYGA. In FORMA-02, one patient experienced arthralgia, a second patient experienced brucellosis and rhinitis and the third patient experienced two cases of ecchymosis, epistaxis, and limb injury. None of these events were considered related to FIBRYGA.

*Reviewer Comment:*

*The efficacy data from pivotal adult study, FIBRES, shows that treatment with FIBRYGA is non inferior to treatment with cryoprecipitate for the treatment of acquired hypofibrinogenemia in bleeding adult cardiac patients. Major safety concerns include TEEs and cardiac disorders; however, these patients are at a high risk of cardiac disorders/complications during surgery and TEEs at baseline. Additionally, data extrapolated from the 3 pediatric studies (FORMA-04, FORMA-02 and FORMA-01) that evaluated FIBRYGA for congenital fibrinogen deficiency) was submitted and shows an acceptable safety profile in patients < 18 years of age. The data submitted from these studies support the use of FIBRYGA in pediatric patients less than 18 years of age with acquired fibrinogen deficiency as the mechanism of action for adults and children is similar.*

*6.1.11.4 Dropouts and/or Discontinuations*

Please see below Section 6.1.12.7 for the details of patient dropouts and discontinuations.

*6.1.11.5 Exploratory and Post Hoc Analyses*

N/A

6.1.12 Safety Analyses

*6.1.12.1 Methods*

The safety population consisted of the mITT population (N=735) from the pivotal, Phase 3, FIBRES study. Three hundred seventy-two patients were randomized to the FIBRYGA arm, and 363 patients were randomized to the Cryoprecipitate arm. All clinical safety data were adjudicated by an IDSMC. Patients received a total of 450 infusions of FIBRYGA and 470 infusions of Cryoprecipitate. Safety was measured by AEs and SAEs during the first 28 days after termination of CPB. Additional safety objectives included the comparison of other secondary safety endpoints including the duration of mechanical ventilation up to postoperative day 28 (measured as duration of ventilation-free days), the duration of ICU stay up to postoperative day 28 and the duration of hospitalization up to postoperative day 28.

Safety was assessed in the FIBRES study by monitoring vital signs, physical examination of patients, routine laboratory testing and collecting AE/SAE information. Safety-related assessments were collected during the run-in period (defined as period prior to the receipt of the investigational agent (either FIBRYGA or cryoprecipitate), treatment period (24 hours from the end of CPB) and follow-up period (28 days from patient enrollment). After postoperative day 28 (in person if in hospital or by phone), the clinical study was considered completed for the patient and no further study-related assessments were preformed, unless safety concerns (e.g.-ongoing AEs) require follow-up.

Recorded AEs could occur at any point during the study, however, recorded TEAEs occurred after patients received FIBRYGA. The severity of AEs was graded as either mild, moderate, or severe and up to the medical judgement of the Investigator and decided on a case-by-case basis. A SAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is another important medical event. The decision of whether an AE is serious was based on medical judgement.

AEs were coded according to MedDRA and the analysis focused on TEAEs. All TEAEs, serious TEAEs and related TEAEs (i.e.-AEs probably or possibly related to the IMP) were summarized and tabulated according to primary system organ class and preferred term.

*6.1.12.2 Overview of Adverse Events*

In total, 1296 TEAEs occurred in 512 patients during the study. Six hundred twenty-three TEAEs occurred in 248 (66.7%) patients in the FIBRYGA group- 249 were considered mild, 233 were considered moderate and 141 were considered severe. Six hundred seventy-three occurred in 264 (72.7%) patients in the cryoprecipitate group- 272 were considered mild, 261 were considered moderate and 185 were considered severe. Two hundred twenty-four treatment-emergent serious adverse events occurred in the FIBRYGA group and 264 TEAEs occurred in the cryoprecipitate group.

The most common class of adverse events was cardiac disorders, with 173 events in 143 (38.4%) patients in the FIBRYGA group and 201 events in 164 (45.2%) patients in the cryoprecipitate group.

The most common adverse reactions (≥5%) observed in the FIBRYGA arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure. The most common adverse reactions observed in the Cryoprecipitate group were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, renal failure, and unlike the FIRBYGA arm, thrombocytopenia, and pneumonia. See **Error! Reference source not found.** below.

**Table 9. Adverse Reactions Reported in More Than 5% of the Patients Following FIBRYGA or Cryoprecipitate Administration in the FIBRES Study**

| **System Organ Class** Preferred Term | **FIBRYGA Patients (N=372) n (%)** | **Cryoprecipitate Patients (N=363) n (%)** |
|---|---|---|
| **Cardiac disorders** | | |
| Atrial fibrillation | 108 (29.0%) | 122 (33.6%) |
| **Blood and lymphatic system disorders** | | |
| Anemia | 58 (15.6%) | 52 (14.3%) |
| Thrombocytopenia | 15 (4.0%) | 20 (5.5%) |
| **Psychiatric disorders** | | |
| Delirium | 56 (15.1%) | 54 (14.9%) |
| **Renal and urinary disorders** | | |
| Acute kidney injury | 29 (7.8%) | 29 (8.0%) |
| Renal failure | 19 (5.1%) | 19 (5.2%) |
| **Hepatobiliary disorders** | | |
| Hepatic function abnormal | 27 (7.3%) | 26 (7.2%) |
| **Infections and infestations** | | |
| Pneumonia | 18 (4.8%) | 19 (5.2%) |

Source: FIBRYGA PI, 2024

**FIBRYGA PI**

In the FIBRYGA group, 224 SAEs occurred in 117 (31.5%) patients; in the cryoprecipitate group, 264 SAEs occurred in 126 (34.7%) patients. The most common class of SAEs was cardiac disorders, with 46 events in 40 (10.8%) patients in the FIBRYGA group and 62 events in 57 (15.7%) patients in the cryoprecipitate group. The median duration of mechanical ventilation for patients in the FIBRYGA group was 1.3 hours and the median duration of mechanical ventilation for patients in the cryoprecipitate group was also 1.3 hours. The median duration of ICU stay was 2.9 hours for the FIBRYGA group and 2.8 hours for the cryoprecipitate group. The median duration of hospitalization was 8.2 days for the FIBRES group and 9 days for the cryoprecipitate group.

*Reviewer Comment:*

- *Overall, the trends in AEs and SAEs on both the FIBRYGA arm and the Cryoprecipitate arm was similar. The incidence of the most common adverse reactions (≥5%) in both arms were similar. There was no different between either group for the median duration of mechanical ventilation and minor differences for both ICU stay and hospitalization. One of the most substantial risks of FIBRYGA is TEEs, please see Section 6.1.12.5 for further details.*

*6.1.12.3 Deaths*

A total of 71 people died in the FIBRES study. Informed consent was not obtained for patient (b) (6) and the research ethics board only approved the collection of SAE data for this patient. Therefore, it was not determined whether or not this patient actually received FIBRYGA, and the treatment is recorded as unknown.

A total of 40 patients died in the FIBRYGA arm and 29 patients died in the Cryoprecipitate arm.

**Table 10. Summary of Timing of Deaths in the FIBRES Study (N=71)**

| Treatment received | Timing of death | | | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Fatal AE started before IMP infusion (meaning it was not a TEAE) | | Fatal AE* was a TEAE | | | | | | | |
| | Up to 28 days after CPB end | | Up to 28 days after CPB end | | More than 28 days after CPB end | | Unknown† | | | |
| | N | % | N | % | N | % | N | % | N | % |
| Fibryga | 8 | 20.00 | 27 | 67.50 | 5 | 12.50 | 0 | 0.00 | 40 | 100.00 |
| Cryoprecipitate | 3‡ | 10.00 | 25 | 83.33 | 2 | 6.67 | 0 | 0.00 | 30 | 100.00 |
| Unknown treatment | 0 | 0.00 | 0 | 0.00 | 0 | 0.00 | 1§ | 100.00 | 1 | 100.00 |
| Total | 11 | 15.49 | 52 | 73.24 | 7 | 9.86 | 1 | 1.41 | 71 | 100.00 |

Source: Adapted from sBLA 125612/133; Applicant's Response to FDA Information Request Dated May 20, 2024, page 2/100
*For patients with multiple fatal AEs documented, at least one fatal AE was a TEAE
†For patient (b) (6) was randomized to FIBRYGA, informed consent was not obtained, and the REB only approved the collection of SAE data. Therefore, the time of death is unknown
‡Includes a major protocol deviation for patient (b) (6) The protocol deviation involved randomization outside of the 24-hour window to eligibility, as the anesthetist thought the patient's second surgery would involve bypass. Although the patient was randomized to receive cryoprecipitate for fibrinogen supplementation, he did not go on the bypass during this second surgery.
§For patient (b) (6) who was randomized to FIBRYGA, informed consent was not obtained, and the REB only approved the collection of SAE data. Therefore, information on whether this patient actually received FIBRYGA, could not be collected and the treatment is recorded as unknown.
Abbreviations: AE, adverse event; CPB, cardiopulmonary bypass; TEAE, treatment-emergent adverse event

*Reviewer Comment:*

*The above table states that 30 patients died in the Cryoprecipitate arm; however, this number includes a major protocol deviation for patient* (b) (6) **The protocol deviation involved randomization outside of the 24-hour window to eligibility. Although patient** (b) (6) **was randomized and received cryoprecipitate for fibrinogen supplementation, they were not put on CPB during surgery, so this death is not included in the FIRBYGA PI or in the below analysis.**

**FIBRYGA Arm**

Forty patients died on the FIBRYGA arm. Eight patients died from a fatal AE that started before the FIBRYGA infusion. Twenty-seven patients died from fatal TEAEs that occurred up to 28 days after CPB end and 5 patients died from TEAEs that occurred more than 28 days after CPB end.

Eight Patients (2.1%) Died From Fatal AEs Which Began Before FIBRYGA Infusion

Seven of these patients died from cardiac complications and one patient died from a cerebral vascular accident (CVA).

- Patient (b) (6) died from congestive heart failure (CHF) which started 10 minutes prior to FIBRYGA infusion and then died 3 days later.
- Patient (b) (6) had a fatal CVA which started 2 hours prior to FIBRYGA infusion and died 27 days later.
- Patient (b) (6) died after cardiac arrest requiring CPR which started 2.5 hours prior to FIBRYGA and died 12 days later.
- Patient (b) (6) died from multi-organ failure which started 3.5 hours prior to FIBRYGA infusion and died 6 days later.

- Patient (b) (6) died from cardiogenic shock that started 6.5 hours prior to receiving FIBRYGA and died 3 hours later.
- Patient (b) (6) also died from cardiogenic shock which started at an unknown time prior to receiving FIBRES and died 4 days later.
- Patient (b) (6) died from biventricular failure which started 4 minutes prior to the FIBRES infusion and died 4 hours later.
- Patient (b) (6) died from active endocarditis which started 30 days prior to FIBRYGA infusion and died 1 day after receiving FIBRYGA.

Twenty-seven Patients (7.3%) Died From Fatal TEAEs That Occurred up to 28 Days After Termination of CPB

- 10 patients died from cardiac causes. (patients (b) (6) (b) (6)
  - Patient (b) (6) died from a cardiac arrest
    - Patient (b) (6) death was a suspected TEE. This patient died 43 minutes after receiving 1 dose of FIBRYGA
  - Patient (b) (6) died from a nonfunctioning heart valve due to stenosis
  - Patient (b) (6) died due to cardiogenic shock/biventricular failure
  - Patient (b) (6) and (b) (6) died due to cardiogenic shock
  - Patient (b) (6) died due to a ventricular septal defect
  - Patient (b) (6) died due to AV disruption
  - Patient (b) (6) died from cardiogenic shock with concurrent elevated liver enzymes
- 1 patient died from distributive shock (patient (b) (6))
- 1 patient died from hemorrhagic shock (patient (b) (6))
- 1 patient died from refractory shock (patient (b) (6))
- 2 patients died from hemorrhage (patients (b) (6) )
  - Patient (b) (6) had concurrent multi-organ failure (patient (b) (6))
- 1 patient died from an upper GI bleed (patient (b) (6))
- 2 patients died from sepsis (patients (b) (6) )
  - 1 with concurrent hepatic failure (patient (b) (6))
  - 1 with concurrent bowel ischemia (patient (b) (6)). This event was also thought to be a TEE.
- 1 patient died from a volvulus (b) (6)
- 2 patients died from a cerebrovascular accident (patients (b) (6)
  - Patient (b) (6) had a stroke 24 hours after receiving FIBRYGA and died 16 days later
  - Patient (b) (6) had a stroke 24 hours after receiving FIBRYGA and died 16 days later
- 1 patient died from spinal cord ischemia (patient (b) (6)
- 2 patients died from intestinal or mesenteric ischemia (patients (b) (6) )
  - Patient (b) (6) died from an ischemic gut which developed 26 hours after the patient's second dose of FIBRYGA
  - Patient (b) (6) died from mesenteric ischemia and hepatic ischemia which developed about 13 hours after this patient received one FIBRYGA and died 12 hours later

- 1 patient died from intra-abdominal ischemia-low volume (patient (b) (6)
- 1 patient died from limb ischemia (patient (b) (6) 12 days after receiving FIBRYGA
- 1 patient died from multi-organ failure (patients (b) (6)

Five Patients (1.3%) Died from TEAEs that Occurred More Than 28 Days After Termination of CPB

- Patient (b) (6) died from complications due to pneumonia about 30 days after receiving one dose of FIBRYGA
- Patient (b) (6) died from hepatic cancer. Ten days after this patient received one dose of FIBRYGA, he experienced acute and severe abdominal pain and a CT scan showed liver cancer with a 3-month prognosis. This patient died 31 days after receiving FIBRYGA
- Patient (b) (6) received 2 doses of FIBRYGA and died 29 days later from E. faecium (vancomycin-resistant enterococci) sepsis
- Patient (b) (6) had a prior myocardial infarction (occurring between 7-29 days prior to surgery and receiving FIBRYGA) and then died about 2.5 months after receiving FIBRYGA from an undocumented fatal AE.
- Patient (b) (6) received one dose of FIBRYGA and on the same day, experienced an AE of multiple organ dysfunction syndrome and died 35 days later. This patient had multiple comorbidities including dyslipidemia, hypertension, atrial fibrillation, CHF, infectious endocarditis, liver disease, renal insufficiency, and coagulopathy all of which may have contributed to the development of multiple organ dysfunction syndrome on the day of surgery.

Nine Patients (2.4%) Received Two Doses of FIBRYGA.

- Of the patients who received two doses of FIBRYGA, four of them died within 24 hours after receiving the second dose.
  - Patient (b) (6) died from hemorrhagic shock 3 hours after receiving a second dose of FIBRYGA. This patient was admitted for emergent surgery six days after an ascending aorta replacement and experienced massive bleeding during surgery and later died in the ICU 2.5 hours after surgery.
  - Patient (b) (6) received two doses of FIBRYGA and died about six hours after receiving the second dose from cardiogenic shock after a cardiac arrest which required CPR.
  - Patient (b) (6) received two doses of FIBRYGA and died 24 hours after the second dose from refractory shock. Patient (b) (6) received two doses of FIBRYGA and died 24 hours later from a hemorrhage that required re-exploration and multi-organ failure.

Eighteen Patients (4.8%) Received One Dose of FIBRYGA

Of these 18 patients:

- Three patients died within 24 hours after receiving FIBRYGA
  - Patient (b) (6) died from AV disruption 19 minutes after receiving FIBRYGA.
  - Patient (b) (6) died from distributive shock 20 hours after receiving FIBRYGA.
  - Patient (b) (6) died from cardiogenic shock 5 hours after receiving FIBRYGA
- One patient died 31 hours after receiving FIBRYGA.
  - Patient (b) (6) died from cardiogenic shock 31 hours after receiving FIBRYGA.

Seven Patients (2%) Died From Either Suspected or Confirmed Thromboembolic Events

- Patient (b) (6) had a stroke 24 hours after receiving FIBRYGA and died 3 days later
- Patient (b) (6) also had a stroke 24 hours after receiving FIBRYGA and died 16 days later
- Patient (b) (6) died from limb ischemia 12 days after receiving FIBRYGA after being readmitted to the hospital for acute limb ischemia. At that time, patient (b) (6) was hemodynamically unstable in the ER, requiring vasopressor infusions to maintain BP. The ischemic limb was the main source of the patient's sepsis which led to death despite the above knee amputation of the right limb secondary to the complete occlusion of the iliac artery.
- Patient (b) (6) died from a cardiac arrest 43 minutes after receiving one dose of FIBRYGA and died
- Patient (b) (6) died from an ischemic gut which started about 4 days after this patient received their second dose of FIBRYGA
- Patient (b) (6) died from mesenteric ischemia and hepatic ischemia which developed about 13 hours after this patient received one dose of FIBRYGA and died 12 hours later
- Patient (b) (6) died from an ischemic gut which developed 26 hours after this patient's second dose of FIBRYGA. CT of this patient's abdomen showed an ischemic bowel with a superior mesenteric embolus and in the patient's subsequent laparotomy, all the small bowel was necrotic and not viable with survival.

**Cryoprecipitate Arm**

Twenty-nine patients died on the Cryoprecipitate arm. Two patients died from a fatal AE that started before the cryoprecipitate infusion. Twenty-five patients died from fatal TEAEs that occurred up to 28 days after CPB end and two patients died from TEAEs that occurred more than 28 days after CPB end.

Two Patients (0.6%) Died From Fatal AEs Which Began Before the Cryoprecipitate Infusion

- Patient (b) (6) died from a cardiac arrest. This patient had multiple cardiac co-morbidities and died 8 days after receiving cryoprecipitate on post-operative day 8
- Patient (b) (6) died from a cerebrovascular accident which occurred one day prior to the patient's surgery. This patient died on post-operative day 12. This event was considered a TEE.

Twenty-five Patients (6.9%) Died From Fatal TEAEs That Occurred up to 28 Days After Termination of CPB

- 1 patient died from vasoplegia syndrome (patient (b) (6))
- 6 patients died from a cerebrovascular accident (patients (b) (6) (b) (6)
  - Patient (b) (6) had concurrent cardiac tamponade requiring re-exploration
  - Patient (b) (6) had concurrent septic shock
  - Patient (b) (6) had concurrent suspected anoxic brain injury
- 4 patients died from multi-organ failure (patients (b) (6)
  - Patient (b) (6) had concurrent delirium and ischemic and had a hemorrhage requiring exploration
- 5 patients died from sepsis (patients (b) (6)

- 4 patients died from cardiogenic shock (patient (b) (6)
  - Patient (b) (6) had concurrent metabolic acidosis, hepatic dysfunction, and hypoglycemia
- 1 patient died from hemorrhagic shock and had concurrent septic shock and hepatic failure (patient (b) (6)
- 1 patient died from cardiac arrest (patient (b) (6)
- 1 patient died from aortic dissection (patient (b) (6)
- 1 patient died from a seizure (patient (b) (6)
- 1 patient died from diffuse anoxic brain injury (patient (b) (6)

Two Patients (0.6%) Died From TEAEs That Occurred More than 28 Days After Termination of CPB

- Patient (b) (6) died from multi-organ failure
- Patient (b) (6) died from aspiration

Ten Patients (2.8%) Died From TEEs

- Patient (b) (6) died from a cerebrovascular accident which occurred one day prior to the patient's surgery. This patient died on post-operative day 12. This event was considered a TEE.
- 6 patients died from a cerebrovascular accident (patients (b) (6) (b) (6)
  - Patient (b) (6) experienced a stroke 4 days after receiving Cryoprecipitate (post-operative day 4) and subsequently deteriorated and experienced hemodynamic collapse
  - Patient (b) (6) experienced a stroke 24 hours after receiving cryoprecipitate. The stroke resulted diffuse ischemic brain injury and the patient died 2 days later
  - Patient (b) (6) experienced a stroke 25 days after receiving cryoprecipitate
  - Patient (b) (6) experienced a stroke 2 days after receiving cryoprecipitate and died 2 days later
  - Patient (b) (6) experienced a stroke 6 days after receiving cryoprecipitate and died 5 days later
  - Patient (b) (6) experienced a stroke 3 days after receiving cryoprecipitate and subsequently died 10 days later
- Patient (b) (6) died from multi-organ failure two hours after receiving cryoprecipitate
- Patient (b) (6) died from a cardiac arrest 3 days after receiving cryoprecipitate
- Patient (b) (6) died from diffuse anoxic brain injury just after receiving cryoprecipitate

*Reviewer's Comment:*

- *Although there were 8 patients on the FIBRYGA arm who died from adverse events which started prior to these patients receiving FIBRYGA, it's difficult to determine if FIBRYGA may have exacerbated their fatal AE. In particular FIBRYGA could have exacerbated Patient (b) (6) fatal CVA, patient (b) (6) fatal cardiac arrest or patient (b) (6) multi-organ failure. It's difficult to discern as all eight of these patients had multiple additional risk factors (e.g.- dyslipidemia, CHF, chronic lung disease, hypertension) and complicated medical histories. Additionally, the PI initially stated that 35 patients died in the FIBRYGA arm, and 27 patients died in the Cryoprecipitate arm. This number was then updated to include patients who died more than 28 days after*

*receiving either FIBRYGA or Cryoprecipitate, bringing the total number of deaths in the FIBRYGA arm to 40 (10.8%) and the total number of deaths in the Cryoprecipitate arm to 29 (8%). The most common cause of death in both arms was cardiac disorders, which is not unexpected due to the nature of the patients' past medical history and the type of cardiac surgery the patients had.*

- *The most common causes of death from fatal TEAEs which occurred up to 28 days after CPB end were cardiac (n=10), stroke (n=2), sepsis (n=2) and intestinal or mesenteric ischemia (n=2) in the FIBRYGA arm. Similarly, the most common causes of death from fatal TEAEs which occurred up to 28 days after CPB end were cerebrovascular accidents (n=6), sepsis (n=5), cardiac (n=5) and multi-organ failure (n=4). It is difficult to determine if FIBRYGA was the cause of death for the patients on the FIBRYGA arm due to the fact that many of these patients had a complicated medical history, which may have put them at risk for more serious complications from surgery and the type of surgery differed from patient to patient, with some surgeries being having more risk than others.*

*6.1.12.4 Nonfatal Serious Adverse Event*

In the FIBRES study, a serious adverse event was defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is another important medical event

SAEs were expected to occur during the FIBRES study due to the nature of the surgeries the patients underwent.

224 serious adverse reactions occurred in 117 (31.5%) patients in the FIBRYGA group compared to 264 serious adverse reactions in 126 (34.7%) patients in the Cryoprecipitate group.

The most common class of SAEs were cardiac disorders, with 46 events in 40 (10.8%) patients in the FIBRYGA group and 62 events in 57 (15.7%) patients in cryoprecipitate group.

<u>FIBRYGA Arm</u>

The cardiac SAEs that occurred in the FIBRYGA arm are:

- Atrial fibrillation (n=4)
- Cardiac arrest (n=5)
- Cardiogenic shock (n=4)
- Congestive heart failure (n=4)
- Heart block (n=4)
- Myocardial infarction (n=2)
- Nonfunctioning valve due to stenosis (n=1)
- Pericardial effusion (n=1)
- Severe mitral valve regurgitation (n=1)
- Supraventricular tachycardia (n=1)
- Cardiac tamponade requiring re-exploration (n=18)

- Ventricular fibrillation (n=1)

The other most common SAEs (>5%) on the FIBRYGA arm are renal failure (n=19, 8.5%), respiratory failure (n=14, 6.3%), hemorrhage requiring re-exploration (n=15, 6.7%), cerebrovascular accidents (n=15, 6.7%), acute kidney injury (n=13, 5.8%), and sepsis (n=12).

Cryoprecipitate Arm

The cardiac SAEs that occurred in the Cryoprecipitate arm are:

- Atrial fibrillation (n=9)
- Cardiac arrest (n=7)
- Cardiac tamponade (n=18)
- Cardiogenic shock (n=7)
- Congestive heart failure (n=5)
- Atrioventricular block (n=7)
- Cardiac failure (n=1)
- Myocardial infarction (n=5)
- Cardiac hematoma (n=1)
- Right ventricular failure (n=3)

The other most common SAEs (>5%) on the FIBRYGA arm are renal failure (n=18), cerebrovascular accident (n=17), acute kidney injury (n=15), respiratory failure (n=15)

For details about serious TEEs, please see Section 6.1.12.5 below.

*Reviewer's Comment:*

*The most common SAEs that occurred on both the FIBRYGA arm and the cryoprecipitate arm were cardiac events and of the cardiac events, the most common one that occurred on both arms was atrial fibrillation. The additional most common SAEs that occurred on both the FIBRYGA arm and the Cryoprecipitate arms were similar. Renal failure, cerebrovascular accidents, respiratory failure, and acute kidney injury were the most common SAEs that occurred on both arms. The most common SAEs on the FIBRYGA arm also included sepsis and hemorrhage requiring re-exploration.*

*6.1.12.5 Adverse Events of Special Interest*

FIBRYGA Arm

There were 32 patients (8.6%) in the FIBRYGA arm who experienced a total of 37 thromboembolic adverse events:

- Cerebrovascular accident (n=17 events)
- Intestinal ischemia (n=4)
- Deep vein thrombosis (n=3)
- Myocardial infarction (n=3)
- Peripheral ischemia (n=2)
- Pulmonary embolism (n=3)
- Transient ischemic attack (n=1)
- Cardiac arrest (n=1)
- Disseminated intravascular coagulation (n=1)
- Ischemic hepatitis (n=1)

- Thrombophlebitis (n=1).

All of the above listed TEEs were considered SAEs except for moderate deep venous thrombosis (DVT), a moderate cerebrovascular accident, mild thrombophlebitis, a mild myocardial infarction, and a mild transient ischemic attack.

Cryoprecipitate Arm

In the cryoprecipitate arm, 45 patients (12.4%) experienced a total of 50 thromboembolic adverse events:

- Cerebrovascular accident (n=18 events)
- Deep venous thrombosis (n=13)
- Cardiac arrest (n=4)
- Myocardial infarction (n=4)
- Intestinal ischemia (n=3)
- Transient ischemic attack (n=1)
- Amaurosis fugax (n=1)
- Aortic thrombosis (n=1)
- Medullar ischemia (n=1)
- Optic ischemic neuropathy (n=1)
- Peripheral artery occlusion (n=1)
- Peripheral ischemia (n=1)
- Vascular graft occlusion (n=1)

Hypersensitivity Reactions

Patient (b) (6) had a mild allergic infusion reaction 2 hours after receiving FIBRYGA. This patient developed extensive urticaria with relative hypotension and atypical normothermia post-surgery for redo aortic valve replacement and primary mitral valve replacement. Transfusion medicine was unable to establish exactly which blood product could have attributed to the reaction. He received 3U Plts, 4U plasma, 4U RBC, 2000 IU PCC, 4g of Fibrinogen, 4mg Factor VIIa. He was treated with diphenhydramine, hydrocortisone, and the hive evanesced.

Transmissible Infectious Agents

No cases of suspicion of viral infection for transfusion-relevant viruses were observed during the FIBRES study.

*Reviewer's Comment:*

> *Initially, the Applicant reported that 26 patients (7%) experienced a total of 27 TEEs in the FIBRYGA arm and 35 patients (9.6%) experienced a total of 39 TEEs on the Cryoprecipitate arm. After further review of the data, the Agency determined there were additional patients who experienced confirmed or potential TEEs for a total of 32 patients (8.6%) who experienced a total of 37 TEEs in the FIBRYGA arm and 45 patients (12.4%) who experienced a total of 50 TEEs.*

The TEEs that occurred on the FIBRYGA arm may have been caused by FIBRYGA, however, it is difficult due to determine due to patients' underlying risk factors for the development of a TEE, the type of the cardiac surgery the patient's had, the risk of TEE events from CPB, and the risk of thrombosis from other blood products used. The most common TEE to occur on either arm was a CVA. Seventeen CVAs occurred on the FIBRYGA arm, and 18 CVAs occurred on the Cryoprecipitate arm.

There was only one mild allergic infusion reaction that could possibly be related to FIBRYGA and no cases of viral infection for transfusion-relevant viruses were observed during the FIBRES study.

*6.1.12.6 Clinical Test Results*

Routine safety laboratory tests comprised hematological parameters measured by the local laboratory at each participating institution within 24 hours of randomization and on postoperative day 7.

Coagulation profiles including PT, partial thromboplastin time (PTT), international normalized ratio and fibrinogen activity were measured before and after administration of FIBRYGA.

Thrombogenicity was not evaluated as a safety outcome in the FIBRES study.

FIBRYGA Arm

Clinically significant laboratory values were reported for 96 (25.8%) of patients. As expected, hemoglobin levels decreased following surgery and then remained constant for 7 days postoperatively for both arms. The white blood cell ( levels fluctuated during the 7 days postoperatively with a nadir on day 5 (10.2 x $10^9$/L. After the termination of CPB, platelet values decreased but rose over the subsequent days (mean =285 x$10^9$/L). Prior to the first FIBRYGA infusion, the mean activated PTT was 31.9 seconds, the mean PT was 15.8 seconds, and the fibrinogen was 2.9 g/L. These values rose over the subsequent days postoperatively. By the time of hospital discharge or Day 28 the mean activated partial thromboplastin time (aPTT) was 40.4 seconds, the PT was 24.4 seconds, and the fibrinogen was 5.2 seconds.

Cryoprecipitate Arm

Clinically significant laboratory values reported for 104 (28.65%) patients. There were similar laboratory patterns in the cryoprecipitate group with no significant differences between the FIBRYGA arm and cryoprecipitate groups in hematocrit, hemoglobin, and platelet levels at all time points.

*Reviewer's Comment:*

> *Clinically significant laboratory values were reported in similar incidences and laboratory patterns in both the FIBRYGA arm (25.8%) and the Cryoprecipitate arm (28.65%). It would be expected that both hemoglobin and platelet levels would drop postoperatively. Hemoglobin levels would then remain constant for 7 days postoperative and platelet levels would continue to rise over the subsequent days postoperatively.*

*6.1.12.7 Dropouts and/or Discontinuations*

**Table 11. Discontinuations From Study**

| Reason for discontinuation | Planned treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Octafibrin (N=415) | | Cryoprecipitate (N=412) | | Total (N=827) | |
| | N | % | N | % | N | % |
| Randomized by mistake without study treatment | 32 | 68.09 | 28 | 52.83 | 60 | 60.00 |
| Treated, but no form of consent available | 6 | 12.77 | 13 | 24.53 | 19 | 19.00 |
| Treated, but no form of consent available (only REB approval to collect SAE data) | 5 | 10.64 | 7 | 13.21 | 12 | 12.00 |
| Death | 3 | 6.38 | 4 | 7.55 | 7 | 7.00 |
| Withdrawal by subject | 1 | 2.13 | 0 | 0 | 1 | 1.00 |
| Screen failure | 0 | 0 | 1 | 1.89 | 1 | 1.00 |
| Total | 47 | 100.00 | 53 | 100.00 | 100 | 100.00 |

Source: Adapted from sBLA 125612/133; Clinical Study Report, page 240/4585
Abbreviations: SAE, serious adverse event

6.1.13 Study Summary and Conclusions

FIBRYGA has demonstrated efficacy and met its primary analysis, demonstrating that FIBRYGA is non-inferior to cryoprecipitate based on the total number of ABPs administered during the first 24 hours after termination of CPB; the mean CBP was 17.0±17.7 versus 17.4±17.0, respectively and an increase fibrinogen levels post administration.

A total of 1296 TEAEs occurred in 512 patients during the study. 623 TEAEs occurred in 248 (66.7%) patients in the FIBRYGA group and 673 occurred in 264 (72.7%) patients in the cryoprecipitate group. A total of 71 people died in the FIBRES study. It was not determined whether or not one patient who died received FIBRYGA as the treatment was recorded as unknown. Forty patients died in the FIBRYGA arm, and 29 patients died in the Cryoprecipitate arm. On the FIBRYGA arm, of the 27 patients who died from TEAEs which occurred up to 28 days after CPB end, the most common causes of death were cardiac (n=10), stroke (n=2), sepsis (n=2) and intestinal or mesenteric ischemia (n=2). Of the 25 patients who died from fatal TEAEs that occurred up to 28 days after CPB end, the most common causes of death were cerebrovascular accidents (n=6), sepsis (n=5), cardiac (n=5) and multi-organ failure (n=4). It is difficult to determine if FIBRYGA was the cause of death for the patients on the FIBRYGA arm due to the fact that many of these patients had a complicated medical history, which may have put them at risk for more serious complications from surgery and the type of surgery differed from patient to patient, with some surgeries being having more risk than others.

The most common SAEs (>5%) that occurred on the FIRBYGA arm were cardiac events, renal failure, respiratory failure, hemorrhage requiring re-exploration, stroke, acute kidney failure and sepsis. The most common SAEs (>5%) that occurred on the Cryoprecipitate arm were cardiac events, renal failure, cerebrovascular accidents, acute kidney injury and respiratory failure. The most common adverse reactions (>5%) observed in the FIBRYGA arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure. Similarly, the most common adverse reactions (>5%) observed in the Cryoprecipitate arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, renal failure, thrombocytopenia, and pneumonia.

The most substantial risk of fibrinogen concentrate products are the development of thrombosis. There was a total of 33 patients (8.6%) in the FIBRYGA arm who experienced a total of 37

TEEs and 45 patients (12.1%) in the Cryoprecipitate arm who have experienced a total of 50 TEEs. The most common TEE that occurred in both arms were cerebrovascular accidents.

Overall, the safety profile of FIBRYGA is acceptable with the benefits outweighing the risks.

## 7. Integrated Overview of Efficacy

Not applicable. The data supporting the proposed indication of fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency was from one study- FIBRES study. The data supporting the proposed indication of fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency was from one study.-

## 8. Integrated Overview of Safety

### 8.1 Safety Assessment Methods

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Safety was assessed in both the FIBRES study and the FORMA-05 study. See above Section 6.1 details of the FIBRES study. FORMA-05 was a prospective, randomized, controlled Phase 2 pilot study investigating the hemostatic efficacy and safety of fibrinogen concentrate (Octafibrin [FIBRYGA]) and Cryoprecipitate as fibrinogen supplementation sources in patients undergoing cytoreductive surgery for pseudomyxoma peritonei (PMP). The primary endpoint of the FORMA-05 study was to compare the overall hemostatic efficacy of *Octafibrin* with that of cryoprecipitate in bleeding patients developing acquired fibrinogen deficiency during cytoreductive surgery for PMP. This study was not evaluated for the overall safety and efficacy of this file.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Please see above Section 1.1 and Section 6.1 for details of the overall exposure and demographics of the FIBRES study.

In the FORMA-05 study, 46 patients were randomized, and 45/46 patients received treatment. The median age was 61 years, with 24/45 (55.6%) female patients and 44/45 (97.8%) classified as White race, with one patient classified as Asian. Based on a homogeneity test between the demographic parameters for sex, race and ethnicity, there were no statistically significant differences between the groups.

The safety population in FORMA-05 consisted of 45 patients: 22 patients in the Octafibrin (FIBRYGA) group and 23 patients in the cryoprecipitate group. At least one dose of Octafibrin (FIBRYGA) was administered to the 22 patients in the Octafibrin arm and at least one dose of cryoprecipitate was administered to the 23 patients in the cryoprecipitate arm.

#### 8.2.3 Categorization of Adverse Events

Please see Section 6.1.12.1 for the categorization of adverse events for the FIBRES study.

In the FORMA-05 study, Safety was assessed by collecting information (e.g., frequency, severity, causality) on AEs), TEAEs, serious AEs (SAEs) and adverse drug reactions (ADRs). In addition, monitoring of vital signs, routine clinical laboratory assessment including of coagulation parameters and viral safety testing were performed.

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

To evaluate the safety of FIBRYGA, pooled safety data is being used from both the FIRBYGA study and the FORMA-05 study. However, both trials have a different indication and study endpoints. Both the FIBRYGA and FORMA-05 trials were adult trials. Additionally, patients in both trials received the initial dose of 4g of FIBRYGA. However, if patients requiring a second dose of FIBRYGA, they were given 4g of FIBRYGA in the FIBRES study and either 4g or 2g of FIBRYGA in the FORMA-05 study.

8.4 Safety Results

8.4.1 Deaths

For details of the patient deaths on the FIBRES study, see above Section 6.1.12.3.

On the FORMA-05 study, no patients died on the FIBRYGA arm, however, one patient died on the cryoprecipitate arm. This patient died from a gastrointestinal anastomotic leak and was deemed unrelated to cryoprecipitate by the investigator.

8.4.2 Nonfatal Serious Adverse Events

For details of the nonfatal SAEs that occurred on the FIBRES study, please see Section 6.1.12.4.

In the FORMA-05 study, a total of 23 SAEs occurred in 18 patients. Six SAEs occurred in 5 patients (22.7%) on the Octafibrin arm, and 17 SAEs occurred in 13 patients (56.5%) on the cryoprecipitate arm.

The six SAEs on the Octafibrin arm included hemodynamic instability, angina pectoris, pneumonia, gastrointestinal stoma complication, tachycardia, and the need of parenteral nutrition.

The 17 SAEs that occurred on the cryoprecipitate arm include 5 pulmonary embolisms, 2 DVT, acute respiratory insufficiency, ventilator-associated pneumonia, pancreatic leak, angina pectoris, hospital acquired pneumonia, wound infection, prolonged ileus, gastric leak, constipation and post procedural bile leak.

8.4.3 Study Dropouts/Discontinuations

For details of the study dropouts and discontinuations in the FIBRES study, please see Section 6.1.12.7.

In the FORMA-05 study, there were no AEs leading to the discontinuation in the FIBRYGA group and there a single AE which led to treatment discontinuation in the cryoprecipitate arm.

8.4.4 Common Adverse Events

For details of the common adverse events that occurred on the FIBRES study, please see Section 6.1.12.2.

FORMA-05

225 AEs occurred in the FIBRYGA arm, and 228 AEs occurred in the cryoprecipitate arm.

FIBRYGA arm- Of the 225 AEs in the FIBRYGA arm-222 were mild, 2 were moderate and 1 was severe. The most common mild TEAEs were gastrointestinal disorders (n=42), respiratory,

thoracic, and mediastinal disorders (n=38), general disorders and administration site conditions (n=26), psychiatric disorders (n=23), cardiac disorders (n=16) and infections and infestations (n=13). The two moderate AEs were decreased hemoglobin and tachycardia. The severe AE was hemodynamic instability.

Cryoprecipitate arm- Of the 228 AEs that occurred in the cryoprecipitate arm, 214 were mild, 12 were moderate and 2 were severe. The most common mild TEAEs include respiratory, thoracic, and mediastinal disorders (n=40), gastrointestinal disorders (n=36), general disorders and administration site conditions (n=24), psychiatric disorders (n=21), infections and infestations (n=15) and cardiac disorders and injury poisoning and procedural complications (both n=12). The moderate AEs were pulmonary embolism (n=4), pancreatic leak (n=2), post-procedural bile leak (n=2), angina pectoris (n=1), acute respiratory failure (n=1), pneumonia (n=1) and pain (n=1). The two severe AEs were pulmonary embolism (n=1) and gastrointestinal anastomotic leak (n=1).

8.4.5 Clinical Test Results

For details of the clinical test results that occurred on the FIBRES study, please see Section 6.1.12.6

Thrombogenicity was not evaluated as a safety outcome in both the FIBRES and the FORMA-05 studies.

In the FORMA-05 study in acquired fibrinogen deficiency, both hematological and clinical chemistry parameters were measured during the preoperative assessment, end of surgery assessment, postoperative assessments (6, 12, 24 and 48 hours, and Day 10), and the end-of-study assessment on Day 21 after surgery/end of hospitalization, whichever was sooner.

The changes in the hematology laboratory results were typical for patients with PMP. These tumors are typically large and there is usually ongoing bleeding and hemostasis intraoperatively. The hemoglobin and hematocrit were normal to low at baseline, decreased during surgery and moderately recovered during the postoperative period, but never reached normal values. Platelet counts were typically normal at baseline, then decreased moderately during surgery, then recovered to above normal postoperatively.

There were no notable differences in biochemistry laboratory values between the FIBRYGA group and the cryoprecipitate group. Most patients started with normal values for ALT, AST, and total bilirubin, however, these values increased during the surgery and normalized over the course of the postoperative period. Greater than 90% of patients had a normal creatinine level at baseline which remained stable during surgery.

8.4.6 Systemic Adverse Events

For details of the systemic adverse events that occurred on the FIBRES study, please see Section 6.1.12.

8.4.7 Local Reactogenicity

Not applicable.

8.4.8 Adverse Events of Special Interest

For details regarding the Adverse Events of Special Interests (AESIs) that occurred on the FIBRES study, please see Section 6.1.12.5.

In the FORMA-05 study, there were no TEEs on the Octafibrin arm, however, there were 7 serious TEEs (pulmonary embolism x5, DVT x2) on the cryoprecipitate arm. No serious infusion related reactions occurred in either arm.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Not applicable.

8.5.2 Time Dependency for Adverse Events

Please see above Section 6.1.12 and Section 8 for details on time dependance for adverse events.

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)

Not applicable.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

Safety of FIBRYGA was evaluated in both the FIBRES (pivotal) and FORMA-05 studies. Please see Section 6.1.13 for a summary of safety conclusions for the FIBRES trial. The additional data from the FORMA-05 study does not change the risks of FIBRYGA and overall the safety data from the FIBRES and FORMA-05 trials is acceptable.

## 9. ADDITIONAL CLINICAL ISSUES

### 9.1 Special Populations

#### 9.1.1 Human Reproduction and Pregnancy Data.

There is no data with FIBRYGA use in pregnant women to determine whether there is a drug-associated risk. Animal reproduction studies have not been conducted with FIBRYGA and it is not known whether FIBRYGA can cause fetal harm when administered to a pregnant woman or affect fertility.

#### 9.1.2 Use During Lactation

There is no information regarding the presence of FIBRYGA in human milk, the effect on the breastfed infant, or the effects on milk production.

#### 9.1.3 Pediatric Use and PREA Considerations

This submission fulfils the PREA for FIBRYGA for the treatment of bleeding in patients with acquired fibrinogen deficiency. Although there were no pediatric patients in the FIBRES study, data extrapolated from 3 pediatric studies (FORMA-04, FORMA-02 and FORMA-01) that evaluated the use of FIBRYGA for bleeding in congenital fibrinogen deficiency was submitted and showed an acceptable safety profile in patients < 18 years of age. This data supports the use of FIBRYGA for bleeding in patients < 18 years of age with acquired fibrinogen deficiency. Please see above Section 6.1.11.3 for further details on pediatric studies of FIBRYGA.

#### 9.1.4 Immunocompromised Patients

Not applicable

#### 9.1.5 Geriatric Use

A total of 177 patients >65 years were treated with FIBRYGA in clinical studies in acquired fibrinogen deficiency, representing 47.6% of the patients in the FIBRYGA group.
Clinical studies of FIBRYGA in congenital fibrinogen deficiency did not include sufficient numbers of patients aged 65 years and over to provide conclusive evidence as to whether or not they respond differently than younger patients.

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

Not applicable

## 10. CONCLUSIONS

FIBRYGA has demonstrated efficacy and met its primary analysis, demonstrating that FIBRYGA is non-inferior to cryoprecipitate based on the total number of ABPs administered during the first 24 hours after termination of CPB; the mean CBP was 17.0±17.7 versus 17.4±17.0, respectively. The fibrinogen level increased from 1.7 ± 0.6 g/L to 2.5 ± 0.6 g/L in the FIBRYGA group and from 1.7 ± 0.6 g/L to 2.3 ± 0.6 g/L for the cryoprecipitate group, representing a mean increase of 0.9 ± 0.4 g/L in the FIBRYGA group and 0.7 ± 0.4 g/L in the cryoprecipitate group.

The most common SAEs (>5%) that occurred on the FIRBYGA arm were cardiac events, renal failure, respiratory failure, hemorrhage requiring re-exploration, stroke, acute kidney failure and

sepsis. The most common SAEs (>5%) that occurred on the Cryoprecipitate arm were cardiac events, renal failure, cerebrovascular accidents, acute kidney injury and respiratory failure. The most common adverse reactions (>5%) observed in the FIBRYGA arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure. Similarly, the most common adverse reactions (>5%) observed in the Cryoprecipitate arm were abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, renal failure, thrombocytopenia, and pneumonia.

The most substantial risk of treatment with fibrinogen concentrates are thrombotic events. Seven patients (2%) died from either suspected or confirmed TEEs and 10 patients (2.8%) on the Cryoprecipitate arm died from suspected on confirmed TEEs. Overall, there were 32 patients (8.6%) in the FIRBYGA arm who experienced a total of 37 TEEs and 45 patients (12.1%) experienced a total of 50 TEEs in the Cryoprecipitate arm. Seven patients (2%) died from either suspected or confirmed TEEs and 10 patients (2.8%) on the Cryoprecipitate arm died from suspected on confirmed TEEs.

There was a total of 40 deaths (10.8%) in the FIBRYGA arm and 29 deaths (8%) in the Cryoprecipitate arm. The most common cause of death in both arms was cardiac disorders, which is not unexpected due to the nature of the patients' past medical history and the type of cardiac surgery the patients had.

Overall, the benefit risk assessment is favorable for approving FIBRYGA for the indication of bleeding in adults and pediatric patients with acquired fibrinogen deficiency.

## 11. Risk-Benefit Considerations and Recommendations

### 11.1 Risk-Benefit Considerations

| Decision Factor | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • Acquired fibrinogen deficiency is a disorder which results in reduced levels of circulating fibrinogen below normal values (<150 mg/dL) that may cause life-threatening bleeding as well as catastrophic complications like intracranial hemorrhage if untreated.<br>• Common causes of acquired fibrinogen deficiency include bleeding, liver disease, plasma exchange therapy, disseminated intravascular coagulation (DIC) and hemophagocytic lymphohistiocytosis (HLH).<br>• Treatment includes on-demand fibrinogen supplementation from either cryoprecipitate or plasma in addition to treating the underlying cause of the acquired fibrinogen deficiency | • Acquired fibrinogen deficiency may be caused by bleeding, liver disease, plasma exchange, DIC or HLH.<br>• Acquired hypofibrinogenemia 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 the treatment of congenital fibrinogen deficiency, however, there are no currently approved products to treat AFD.<br>• Available accepted treatments for AFD include plasma-derived fibrinogen concentrates, which may carry risk of infection and hypersensitivity. | • FIBRYGA utilizes multiple, advanced manufacturing processes to purify and standardize the product and inactivate most known infectious agents.<br>• Thrombotic risks of exogenous fibrinogen concentrate are intrinsic to its mode of action |
| **Clinical Benefit** | • Data from the FIBRES trial was submitted to demonstrate the safety and effectiveness of the treatment of acute bleeding episodes in patients with acquired hypofibrinogenemia with the primary efficacy endpoint of the total number of units of ABPs (RBCs, pooled or apheresis platelets, and plasma) administered during the 24 hours after termination of CPB.<br>• FIBRYGA has been previously shown to have acceptable safety and sufficient efficacy to be approved for the on-demand treatment of bleeding in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. | • FIBRYGA was demonstrated to be non-inferior to cryoprecipitate based on the total number of ABPs administered during the first 24 hours after the termination of CPB.<br>• There was an increase in fibrinogen levels post administration of the product.<br>• |
| **Risk** | • In studies of FIBRYGA use for bleeding management and perioperative management, thromboses were observed.<br>• The most common adverse reactions to treatment with FIBRYGA (>5%) in patients with acquired fibrinogen deficiency are abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure.<br>• The most common adverse reactions to treatment with FIBRYGA (>5%) in patients with congenital fibrinogen deficiency are nausea, vomiting, pyrexia | • FIBRYGA has an acceptable safety profile, and the risks are addressed in the package insert<br>• Evidence suggests that infectious risks and hypersensitivity risks from FIBRYGA treatment occur and included in the label. |

| | | |
|---|---|---|
| **Risk Management** | • The most substantial risk of treatment with fibrinogen concentrates are thrombotic events in addition to hypersensitivity reactions and potential infectious risks.<br>• Risk management plans include the warnings and precautions and common adverse reactions listed in FIBRYGA's prescribing information | • The FIBRYGA package insert, along with routine medical management and pharmacovigilance are adequate to manage risk.<br>• The data do not support the need for a risk evaluation and mitigation strategy (REMS). |

11.2 Risk-Benefit Summary and Assessment

FIBRYGA has demonstrated efficacy and met its primary analysis, demonstrating that FIBRYGA is non-inferior to cryoprecipitate based on the total number of ABPs administered during the first 24 hours after termination of CPB; the mean CBP was 17.0 ±17.7 versus 17.4±17.0, respectively. The fibrinogen level increased from 1.7 ± 0.6 g/L to 2.5 ± 0.6 g/L in the FIBRYGA group and from 1.7 ± 0.6 g/L to 2.3 ± 0.6 g/L for the cryoprecipitate group, representing a mean increase of 0.9 ± 0.4 g/L in the FIBRYGA group and 0.7 ± 0.4 g/L in the cryoprecipitate group.

The safety profile is acceptable. The most common TEAEs were the most common adverse reactions to treatment with FIBRYGA (>5%) in patients with acquired fibrinogen deficiency are abnormal hepatic function, acute kidney injury, anemia, atrial fibrillation, delirium, and renal failure. The most substantial risk of treatment with fibrinogen concentrates are thrombotic events. Overall, there were 32 patients (8.6%) in the FIRBYGA arm who experienced a total of 37 TEEs and 45 patients (12.1%) experienced a total of 50 TEEs in the Cryoprecipitate arm.

There was a total of 40 deaths (10.8%) in the FIBRYGA arm and 29 deaths (8%) in the Cryoprecipitate arm. The most common cause of death in both arms was cardiac disorders, which is not unexpected due to the nature of the patients' past medical history and the type of cardiac surgery the patients had.

The benefit risk profile of FIBRYGA is favorable.

11.3 Discussion of Regulatory Options

The available data support traditional approval for the indication of FIBRYGA for fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency.

The total number of ABPs administered during the first 24 hours after termination of CBP is a clinically meaningful for fibrinogen supplementation in bleeding patients with acquired fibrinogen deficiency. FIBRYGA met the pre specified NI margin is the basis for the traditional approval.

11.4 Recommendations on Regulatory Actions

The clinical team considered the benefit observed in the increase in fibrinogen granting traditional approval to FIBRYGA for the supplementation of fibrinogen in bleeding patients with acquired fibrinogen deficiency.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well controlled clinical study, with supportive evidence from the initial clinical investigations. The evidence of treatment effect in the study is based on the clinically meaningful total number of ABPs administered during the first 24 hours after termination of CBP and increase in fibrinogen levels post administration of FIBRYGA. The safety profile is acceptable and favors a positive benefit-risk profile.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends traditional approval of FIBRYGA for the supplementation of fibrinogen in bleeding patients with acquired fibrinogen deficiency.

Based on the available data, the clinical reviewers recommend traditional approval of FIBRYGA for the supplementation of fibrinogen in bleeding patients with acquired fibrinogen deficiency.

11.5 Labeling Review and Recommendations

The revised package insert was reviewed, commented on, and revised by the appropriate discipline reviewers. FDA's Advertising and Promotional Labeling Branch conducted its review from a promotional and comprehension perspective. Labeling issues have successfully been resolved with the Applicant.

Key changes included:

- Revising the efficacy data presented for the interim analysis
- Deleting the superiority claim in the label
- Updating the safety section including the thrombotic events, patient deaths that occurred on the FIBRES study and adverse reactions reported in more than 5% of patients following FIBRYGA or cryoprecipitate administration in the FIBRES study.

11.6 Recommendations on Postmarketing Actions

No postmarketing requirement or postmarketing commitment studies are requested at this time. Review of the clinical data found no safety concern that would necessitate a Risk Evaluation and Mitigation Strategy, a postmarketing commitment, or a required postmarketing study that is specifically designed to evaluate safety as a primary endpoint. All risks were included in the label.