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Application Type	BLA Supplement
STN	125612/133
CBER Received Date	01/30/2024
PDUFA Goal Date	07/31/2024
Division / Office	OBPV
Committee Chair	Megha Kaushal, MD Courtney Johnson, MD
Clinical Reviewer(s)	Megha Kaushal, MD– Clinical Efficacy Courtney Johnson, MD- Clinical Safety
Project Manager	Shalini Seetharaman, MS
Priority Review	Yes
Reviewer Name(s)	Yuyin Shi, PhD Staff Fellow, TEB2/DB/OBPV
Review Completion Date / Stamped Date	July 12, 2024
Supervisory Concurrence	Lin Huo, PhD, Team Lead, TEB2/DB/OBPV
	Lihan Yan, PhD, Branch Chief, TEB2/DB/OBPV
Applicant	OCTAPHARMA Pharmazeutika Produktionsges. m.b.H.
Established Name	Fibrinogen (Human)
(Proposed) Trade Name	FIBRYGA
Pharmacologic Class	Hemostatic
Formulation(s), including Adjuvants, etc	Fibrinogen concentrate (human)
Dosage Form(s) and Route(s) of Administration	A highly purified, lyophilized human plasma fibrinogen concentrate for intravenously use
Dosing Regimen	For adults: 4g For adolescents age ⩾ 12 years: 50 mg/kg body weight For children age <12 years: 70 mg/kg body weight
Indication(s) and Intended Population(s)	Fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency

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GLOSSARY

ABP	Allogeneic Blood Products
ACB	Aortocoronary Bypass
AE	Adverse Event
BLA	Biologics License Application
BMI	Body Mass Index
CI	Confidence Interval
CPB	Cardiopulmonary Bypass
CSR	Clinical Study Report
FFP	Fresh Frozen Plasma
ICU	Intensive Care Unit
IDSMC	Independent Data Safety Monitoring Committee
IMP	Investigational Medicinal Product
IQR	Interquartile Range
IV	Intravenous
mITT	Modified Intention-To-Treat
NI	Non-inferior
PMP	Pseudomyxoma Peritonei
PP	Per-Protocol
REB	Research Ethics Board
SAE	Serious Adverse Event
SAF	Safety Population
SD	Standard Deviation
SDM	Surrogate Decision Maker
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
UDPB	Universal Definition of Perioperative Bleeding

1. Executive Summary

This is a biologics license application (BLA) efficacy supplement intended to expand the indication of FIBRYGA (also referred to as Octafibrin) to include fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency. Octafibrin is a plasma-derived, double virus inactivated/eliminated, highly purified concentrate of freeze-dried human fibrinogen. It was originally approved by the FDA in 2017 for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.

The primary evidence of efficacy and safety is based on the results from the Phase 3 study FIBRES. Results from another study FORMA-05 was also provided as supportive safety evidence. This statistical review memo focuses on the analyses of the FIBRES study only.

FIBRES was a pragmatic, prospective, multicenter, randomized, active-control, single-blinded, non-inferiority phase 3 trial in adult cardiac surgical patients. The study planned to enroll 1200 evaluable patients and employed a group-sequential design with 1 interim analysis after 600 patients have been recruited and 1 final analysis. The primary efficacy objective of this study was to demonstrate that the fibrinogen concentrate Octafibrin is non-inferior (NI) to cryoprecipitate. The primary efficacy endpoint was the total number of units of allogeneic blood products (ABPs) administered during the first 24 hours after termination of cardiopulmonary bypass (CPB). The NI margin was 1.20 for the ratio of ABPs between the Octafibrin and the cryoprecipitate groups.

A total of 605 treated patients were included in the interim primary efficacy analysis: 302 in the Octafibrin group and 303 in the cryoprecipitate group. The estimated ratio of ABPs between the Octafibrin group and the cryoprecipitate group was 0.9822, using the ordinary Poisson regression. A one-sided hypothesis test with a type I error probability control at α_1=0.00258 gave a 99.742% upper CI limit of 1.0375, below the 1.20 NI margin, demonstrating non-inferiority ($p<0.0001$). Because of dispersion in observed data, two adjusted models (statistically more appropriate) were employed and resulted in the upper CI limits marginally exceeding 1.20. Nevertheless, the study was stopped early based on the recommendation of the IDSMC for meeting the criterion for non-inferiority at the interim analysis.

In the final study report submitted with this sBLA, the updated (refer to as “final” by the applicant) primary efficacy analysis included 735 patients, with 372 in the Octafibrin group and 363 in the cryoprecipitate group. The estimated ratio of ABPs was 0.9569 and the nominal 97.5% upper CI limits ranged from 0.9914 to 1.1121 across three statistical models. These results supported the non-inferiority conclusion but did not support the superiority conclusion as the upper bounds from the more appropriate models were above 1.0.

As for safety, of the 735 patients in the study, 224 serious adverse events (SAEs) occurred in 117 (31.5%) patients in the Octafibrin group and 264 SAEs occurred in 126 (34.7%) patients in the cryoprecipitate group. In the period from termination of CPB to

postoperative Day 28, 35 (9.41%) patients in the Octafibrin group and 27 (7.44%) patients in the cryoprecipitate group died.

Conclusion and Recommendation

Overall, the FIBRES study data supported the non-inferiority of FIBRYGA compared to cryoprecipitate as fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency. However, the data do not support a conclusion of superiority of FIBRYGA to cryoprecipitate in this indication. I defer to the clinical team on the acceptance of the safety profile of FIBRYGA.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Coagulopathy leading to excessive bleeding is a serious complication of cardiac surgery requiring cardiopulmonary bypass (CPB). Occurring in more than 10% of cases, it frequently necessitates the transfusion of large amounts of allogeneic blood products (ABPs) and is associated with an increased risk of adverse outcomes, such as multi-organ failure and death. While the causes of coagulopathy are usually multifactorial, acute acquired hypofibrinogenemia – defined as an acute drop in plasma fibrinogen concentration – is believed to be a key factor.

Fibrinogen is a critical component of the coagulation cascade as it is both a precursor for fibrin and a cofactor that enhances platelet aggregation. Unlike other coagulation factors, it does not have a large reserve margin, and a modest drop in fibrinogen levels to <1.5–2.0 g/L impairs coagulation and increases bleeding complications.

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

There are two primary sources of concentrated fibrinogen available for fibrinogen supplementation: cryoprecipitate and purified human plasma-derived fibrinogen concentrate. Cryoprecipitate is currently the mainstay of therapy in North America, but it has several important limitations: 1) the amount of fibrinogen in each unit of cryoprecipitate is highly variable; 2) thawing and pooling of cryoprecipitate is time-consuming and labor-intensive; 3) cryoprecipitate is not a purified product and has many constituents aside from fibrinogen, some of which may be deleterious. Human plasma-derived fibrinogen concentrate is currently the mainstay of therapy for acquired hypofibrinogenemia in much of Europe. In North America, however, this therapy is only approved for the treatment of congenital hypofibrinogenemia and afibrinogenemia.

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

Octafibrin (under the trade name FIBRYGA) was approved in the United States (US) on June 7, 2017, for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. FIBRYGA has also been approved in multiple European countries and Canada.

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

FIBRES was not conducted under an IND, and was conducted in Canada. A pre-BLA meeting was requested by the applicant on July 05, 2023 (CRMTS #15142) and a written response was issued to the applicant by the FDA on September 20, 2023, in which FDA recommended that the sponsor submit a supplement to the BLA for review with the revised indication.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

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

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

5.1 Review Strategy

This review memo focuses on analyses of the Phase 3 FIBRES Study.

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

The following documents in the BLA 125612/133 were reviewed:

- 1.14 Labeling
- 2.5 Clinical Overview
- 2.7 Clinical Summary
- 5.3.5.1 Clinical Study Report (CSR) for FIBRES and supporting documents and datasets.
- Amendment - response to IR dated February 24, 2024
- Amendment - response to IR dated February 28, 2024

5.3 Table of Studies/Clinical Trials

Clinical efficacy and safety were assessed in the Phase 3 study FIBRES and the Phase 2 supportive study FORMA-05. A summary of these two studies is provided in Table 1.

Table 1: Summary of Clinical Studies in the sBLA

Study No. Status	**Population/ No. of Patients/ Planned Age (Enrolled Age)**	**Design/ Study Site/ Location/ Study Period**	**Test Product(s)/ Dosage Regimen/ Duration of Treatment**	**Endpoints**
FIBRES Completed	Bleeding cardiac surgical patients in whom fibrinogen supplementation is ordered according to accepted clinical standards. N=735 Median (range): 64.0 years (17-88)	Prospective Multicentre Randomised Active control Non-inferiority Phase 3 11 centers in Canada Start: 23-Feb 2017 End: 28-Nov-2018	Octafibrin Cryoprecipitate Each time fibrinogen supplementation was ordered within the 24 hours after termination of CPB, patients received either cryoprecipitate (1 dose = 10 units = approx. 4 g) or purified fibrinogen concentrate (1 dose = 4 g) infused in 10 minutes.	*Primary endpoint* Total number of units of ABPs administered during the first 24 hours after termination of CPB. *Secondary endpoints* Total number of units of ABPs administered within 24 hours after the start of cardiac surgery, and from the beginning of surgery until 7 days after surgery or discharge, if earlier; major bleeding using the validated UDPB; effect on fibrinogen levels before and after the first dose of fibrinogen supplementation; safety profiles of Octafibrin and cryoprecipitate
FORMA-05 Completed	Bleeding patients with acquired fibrinogen deficiency during cytoreductive surgery for PMP N=45 ≥18 years (34-76 years)	Prospective Randomised Open-label Comparator-controlled (with cryoprecipitate as comparator) Phase 2 One center in the UK	Octafibrin Cryoprecipitate Dosage Regimen: *Pre-emptive:* the first dose of Octafibrin (4 g) or cryoprecipitate (2 pools of 5 units each) administered based on clinical judgement for fibrinogen supplementation made at the 'bleeding risk assessment' time point, which took place approximately 60–90 min after	*Primary endpoint* Frequency of the overall hemostatic success adjudicated by the IDMEAC *Secondary endpoints* *Efficacy:* intraoperative and postoperative hemostatic efficacy; capability to correct acquired fibrinogen deficiency in terms of plasma fibrinogen concentration and FIBTEM A20; dose, duration and timing for

		Start: 13-Mar-2017 End: 20-Jul-2018	the beginning of surgery, before 2L of blood were lost. *Intraoperative:* A FIBTEM A20 of 12 mm or less triggered the administration of either 4 g Octafibrin or 2 cryoprecipitate pools of 5 units each. *Up to 24-hour Postoperative:* A FIBTEM A20 of 12mm or less triggered the administration of either 2 g Octafibrin or 1 cryoprecipitate pool of 5 units. *Beyond 24-hour postoperative:* Subjects in both treatment groups were treated only with cryoprecipitate for fibrinogen supplementation. Administration was triggered by either a Clauss plasma fibrinogen concentration of 2g/L or less or FIBTEM A20 of 12mm or less.	delivery of fibrinogen substitution; coagulation profiles; critical care outcomes including transfusion *Safety:* Safety profiles of Octafibrin and cryoprecipitate

Abbreviations: APB = allogeneic blood product; CPB = cardiopulmonary bypass; UDPB = universal definition of perioperative bleeding; FIBTEM A20 = clot amplitude at 20 minutes in the thromboelastometric FIBTEM test; IDMEAC = Independent Data Monitoring and Endpoint Adjudication Committee; PMP = pseudomyxoma peritonei.
Source: Adapted from sBLA 125612/133; Clinical Overview, Table 1

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 FIBRES Study

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

6.1.1 Objectives

The primary objective of this study was to demonstrate that the fibrinogen concentrate Octafibrin is non-inferior to cryoprecipitate. The primary efficacy endpoint was the total number of units of ABPs administered during the first 24 hours after termination of CPB.

The 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 1 hour before and 1 hour after fibrinogen supplementation.
- Comparison of safety as measured by adverse events (AEs) and serious adverse events (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

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

The FIBRES study planned to enroll 1200 evaluable patients and employed a group-sequential design that involves 1 pre-planned interim analysis after 600 patients have been recruited. The study enrollment may be stopped after the interim analysis for safety or futility reasons or if non-inferiority was demonstrated.

Patients were randomized to receive equivalent doses, in terms of fibrinogen content, of either fibrinogen concentrate (Octafibrin) or cryoprecipitate. Efficacy data were collected up to 7 days after the start of surgery, while safety was monitored throughout the study, up to 28 days after termination of CPB.

6.1.3 Population

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).

6.1.4 Study Treatments or Agents Mandated by the Protocol

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.

Octafibrin or cryoprecipitate was administered by intravenous (IV) injection using an established IV route. Octafibrin 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

The study was conducted at 11 sites in Canada.

6.1.7 Surveillance/Monitoring

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). Please refer to the clinical review for more details on study surveillance and monitoring.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint
The total number of ABP units (RBCs, pooled and apheresis platelets, and plasma) used within 24 hours after termination of CPB.

Secondary Efficacy Endpoints
- Total number of units of ABPs administered from the start of cardiac surgery until 7 days after surgery or discharge.
- Distribution of major bleeding type, using the validated Universal Definition of Perioperative Bleeding (UDPB) in cardiac surgery.
- Change in plasma fibrinogen concentration (measured using the Clauss assay) before and after fibrinogen supplementation for first and subsequent doses.
- Total number of units of ABPs administered within 24 hours after the start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets, and plasma.

Secondary Safety Endpoints
- Detailed list of AEs and SAEs, collected up to postoperative Day 28 and compared numerically between the two groups.
- Composite of selected AEs, i.e., death, myocardial infarction, stroke, acute liver injury, acute kidney injury and thromboembolic events, compared between the groups up to postoperative Day 28
- Other secondary safety endpoints compared between groups:
    - Duration of mechanical ventilation (measured as duration of ventilation and ventilator-free days up to postoperative Day 28)
    - Duration of ICU stay up to postoperative Day 28
    - Duration of hospitalization up to postoperative Day 28.

Success Criterion
This study was designed to demonstrate that Octafibrin is clinically not inferior to the cryoprecipitate with respect to total number of units of ABPs administered within 24

hours after termination of CPB. The success criterion was defined as the upper limit of the confidence interval (CI) for the ratio of ABPs between the Octafibrin group and the cryoprecipitate group does not exceed the inferiority margin of 1.2, with a one-sided type I error control at $\alpha = 0.025$. The null and the alternative hypotheses were defined as the following in the statistical analysis plan (SAP):

$$H_0: \frac{\mu_F}{\mu_C} \geq (1+\delta) \quad v.s. \quad H_1: \frac{\mu_F}{\mu_C} < (1+\delta),$$

where $1+\delta$ is the NI margin, μ_F and μ_C denote the mean number of units of ABPs in the Octafibrin and cryoprecipitate treatment groups, respectively.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size and NI margin Determination

Based on the one-sided overall type I error probability control at α = 0.025, simulations have been performed to study the power of the above test for different sample sizes and values of the NI margin.

Random samples for the total amount of ABP units have been generated based on an empirical distribution function with a mean of 16 ABP units and a standard deviation of 14 units. Ten thousand studies for each different sample size were simulated. Based on the assumption of comparable efficacy, identical means and standard deviations were used for both treatment groups.

Using the data described above, an empirical power of >90% was expected with a sample size of at least 550 patients per treatment group if δ of 0.20 was chosen. For smaller values of δ, no sufficient power could be attained with operationally feasible sample sizes. The choice of the non-inferiority margin δ = 0.20 was also due to the substantial intrinsic variation in the primary endpoint that has to be expected from previous studies reflecting current clinical practice. To account for about 10% randomized patients would not be treated after randomization or for whom the endpoint couldn't reliably be obtained, it was planned to conduct the study with a maximum sample size of 600 patients in each treatment group.

Analysis Population

The modified intention-to-treat (mITT) population included all randomized patients who received at least one dose of IMP and who met both of the following criteria:

- Unrestricted consent available by patient, surrogate decision maker (SDM) or research ethics board (REB), and
- Performed procedure was cardiac surgery.

The treatment group was defined according to the randomization (rather than the actual treatment received).

The per-protocol (PP) 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

Primary Efficacy Endpoint Analyses

The primary efficacy variable was the total number of ABP units (RBCs, pooled and apheresis platelets, and plasma) used within 24 hours after termination of CPB. Apheresis/non-apheresis units were counted as their equivalent allogeneic units:

- for platelets, 1 apheresis unit = 4 allogeneic units, 1 non-apheresis unit = 4 allogeneic units;
- for plasma, 1 apheresis unit = 2 allogeneic units, 1 non-apheresis unit = 1 allogeneic unit;
- for RBC: 1 unit = 1 allogeneic unit.

Poisson regression model was to be used to assess the primary hypothesis as stated in Section 6.1.8 for the interim and updated final analyses, model assumptions (e.g., assumptions about the deviance) were to be checked during the analyses. The point estimate and one-sided CI for the ABP ratio were to be presented. The primary efficacy endpoint analysis was to be performed on the mITT population and a secondary analysis was to be performed for the PP population.

Superiority was to be tested in the case of non-inferiority was demonstrated in the mITT and the PP population:

$$H_0: \frac{\mu_F}{\mu_C} \geq 1 \quad v.s. \quad H_1: \frac{\mu_F}{\mu_C} < 1,$$

where μ_F and μ_C denote the mean number of units of ABPs in the Octafibrin and cryoprecipitate treatment groups, respectively. Since the test for superiority would only be performed if non-inferiority had been demonstrated previously, no adjustment of type I error was necessary.

Interim Analysis

One unblinded interim analysis after 600 patients have been enrolled was to be conducted, allowing for an early stopping for demonstrated non-inferiority of FIBRYGA or an early stopping due to futility. A sequential design with α spending function according to O'Brien-Fleming method was used. After interim analysis, a positive outcome for non-inferiority may be claimed and enrolment may be stopped if the null hypothesis was rejected in the mITT population based on the adjusted one-sided significance level of $\alpha_1 = 0.00258$. A full final analysis including all study data was to be performed and reported if enrolment is stopped after the interim analysis. Also, at the time of this interim analysis the study enrolment may be stopped if the predictive power for the test of non-inferiority at the final stage is less than 0.25 (futility stop).

Secondary Efficacy Endpoints Analyses

- The total number of ABPs within 7 days/discharge and the different subtypes of ABPs were to be analyzed analogously to the primary endpoint, presenting point estimates and two-sided 95% CIs in addition to descriptive statistics.
- Frequency distributions of the major bleeding type according to UDPB were to be presented for each treatment group.

- Change in fibrinogen plasma level was to be tested with the Wilcoxon rank-sum test between the two treatment groups. The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the Octafibrin and cryoprecipitate treatment groups and the corresponding 95% CI were to be calculated.

Subgroup Analyses for Efficacy

Subgroup analyses of the primary endpoint by sex, age group, race and the following subgroups were to be performed: non-elective surgery; complex surgery (procedures other than isolated aortocoronary bypass [ACB], single valve repair/replacement, or isolated repair of atrial septal defects); and all patients except those who were in critical state before surgery, as determined by adjudicators who were blinded to the IMP.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

At the time of the 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.

In the updated analysis, 827 patients were randomized to receive Octafibrin (N=415) or cryoprecipitate (N=412). Thirty-two patients in the Octafibrin group and 29 patients in the cryoprecipitate group were excluded from the mITT population because of not receiving IMP, while 11 patients in the Octafibrin group and 20 patients in the cryoprecipitate group were excluded because of no available consent. Table 2 provides the sample sizes of the analysis populations.

Table 2: Analysis Population

	Octafibrin, N	**Cryoprecipitate, N**	**Overall, N**
Interim mITT	302	303	605
Interim PP	296	302	598
Updated mITT	372	363	735
Updated PP	364	361	725

Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 14.1-1; IA draft 01 on 10/17/2018, Table 14.1-1

6.1.10.1.1 Demographics

The demographic characteristics are summarized by treatment groups for the updated mITT in Table 3. Subjects aged between 17 and 88 years. Around 70% of subjects were male. Around 71% of subjects were White. Median body mass index (BMI) was 22.51 with a range of (11.11, 52.63). The demographics of the two study groups were similar.

Table 3: Demographics (Updated mITT; N=735)

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)

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

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A total of 62.10% of the Octafibrin group and 64.74% of the cryoprecipitate group underwent elective surgery. The surgery was classed as complex for 71.77% of the Octafibrin group and 71.63% of the cryoprecipitate group. A slightly higher proportion of patients in the Octafibrin (16.9%) group than the cryoprecipitate group (10.5%) were adjudicated to be in a critical state before surgery. (Table 4).

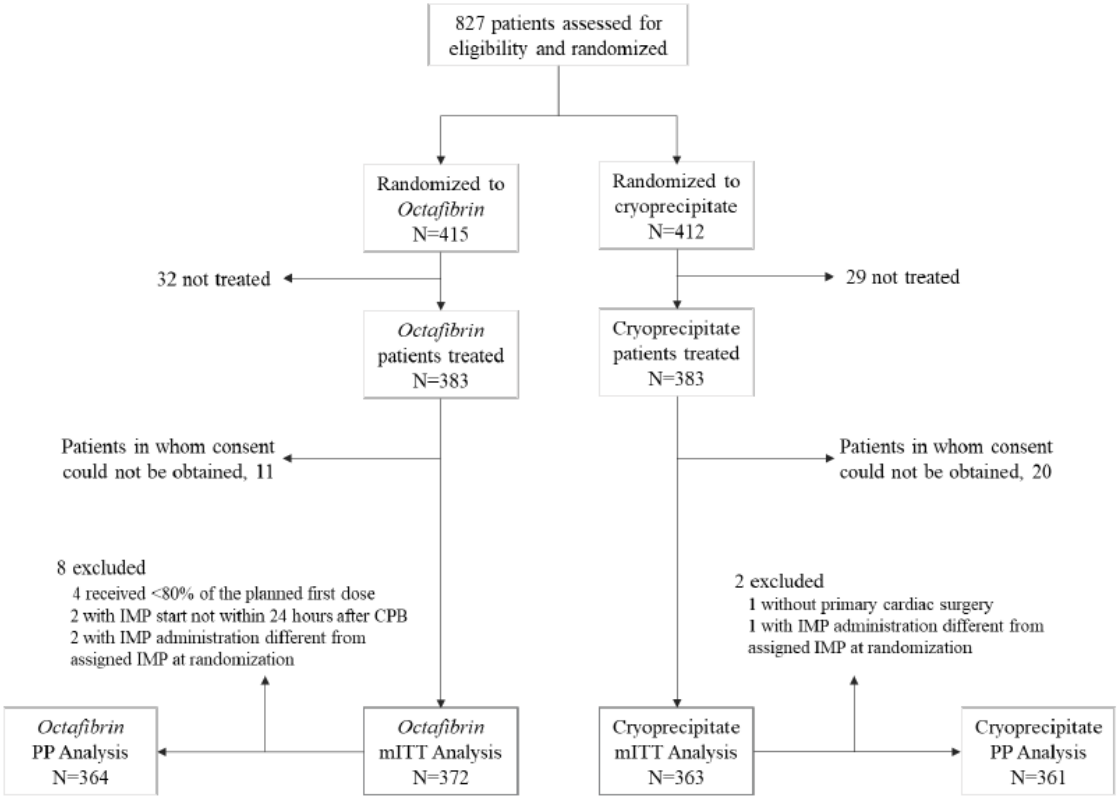
Table 4: Selected Surgery Characteristics (Updated mITT; N=735)

Category	Octafibrin N=372	Cryoprecipitate N=363	Total N=735
Complexity of surgery, n (%)			
Complex	267 (71.77)	260 (71.63)	527 (71.70)
Non-complex	105 (28.23)	103 (28.37)	208 (28.30)
Surgery urgency status, n (%)			
Elective	231 (62.10)	235 (64.74)	466 (63.40)
Non-elective	141 (37.90)	128 (35.26)	269 (36.60)
State before surgery, n (%)			
Critical	63 (16.94)	38 (10.47)	101 (13.74)
Non-critical	309 (83.06)	325 (89.53)	634 (86.26)

Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 9

6.1.10.1.3 Subject Disposition
A summary of subject disposition for all available data is presented in Figure 1.

Figure 1: Subject Disposition



Abbreviations: CPB = cardiopulmonary bypass; IMP = investigational medicinal product; mITT = modified intention-to-treat; PP = per-protocol.
Source: sBLA 125612/133; Clinical Study Report, Figure 2

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

<u>Interim results with 605 subjects:</u>
A total of 605 treated patients were included in the interim primary efficacy analysis: 302 in the Octafibrin group and 303 in the cryoprecipitate group. The means (SDs) of ABPs transfused in the Octafibrin group and cryoprecipitate group were 17.08 (17.69) and 17.39 (17.02), respectively, resulting in a ratio of 0.9822 using the ordinary Poisson regression. A one-sided hypothesis test with a type I error probability control at $\alpha_1 = 0.00258$ gave a 99.742% upper CI limit of 1.0375**,** below the 1.20 NI margin, demonstrating non-inferiority (p<0.0001).

As the data were found to be over-dispersed, non-inferiority was additionally evaluated using deviance scaled Poisson regression and negative binomial regression methods. In both cases the 99.742% upper CI limits exceeded NI margin 1.20: 1.2049 (p=0.0031) in deviance scaled Poisson regression and 1.2460 (p=0.0093) in negative binomial regression. Analysis results using interim PP were similar to results using interim mITT

(Table 5). Nevertheless, the study was stopped early based on the recommendation of the IDSMC for meeting the criterion for non-inferiority at the interim analysis.

Table 5: Interim Primary Efficacy Endpoint Analysis on the ABPs Units Used Within 24 hours After Termination of CPB

Interim mITT (N=605)		
	Estimate of mean ratio	**99.742% Upper CI (p-value)**
Ordinary Poisson	0.9822	1.0375 (<0.0001)
Deviance Scaled Poisson	0.9822	1.2049 (0.0031)
Negative Binomial	0.9822	1.2460 (0.0093)
Interim PP (N=598)		
	Estimate of mean ratio	**99.742% Upper CI (p-value)**
Ordinary Poisson	0.9903	1.0463 (<0.0001)
Deviance Scaled Poisson	0.9903	1.2161 (0.0045)
Negative Binomial	0.9903	1.2573 (0.0122)

Source: FDA statistical reviewer's analysis.

Updated results with 735 subjects:

An updated (refer to as "final" by the applicant) primary efficacy analysis based on all available data (N=735; 372 in the Octafibrin group and 363 in the cryoprecipitate group), including additional data beyond the interim analysis, was conducted. The means (SDs) of ABPs transfused in the Octafibrin group and cryoprecipitate group were 16.29 (16.70) and 17.03 (16.05), respectively, resulting in a ratio of 0.9569. A one-sided hypothesis test with significance level of 2.5% gave a 97.5% upper CI limit of 0.9914, demonstrating non-inferiority ($p<0.0001$), and subsequently, superiority ($p=0.0074$). Analysis results using deviance scaled Poisson regression and negative binomial regression agrees with the non-inferiority, while superiority was not supported as both upper CI limits exceeded 1.0. These results were supported by analysis of the PP population, except superiority was no longer demonstrated using the Poisson regression (Table 6).

Table 6: Updated Primary Efficacy Endpoint Analysis on the ABPs Units Used Within 24 hours After Termination of CPB

Updated mITT (N=735)		
	Estimate of mean ratio	**97.5% Upper CI (p-value)**
Ordinary Poisson	0.9569	0.9914 (<0.0001)
Deviance Scaled Poisson	0.9569	1.0875 (0.0003)
Negative Binomial	0.9569	1.1121 (0.0016)
Updated PP (N=725)		
	Estimate of mean ratio	**97.5% Upper CI (p-value)**
Ordinary Poisson	0.9704	1.0056 (<0.0001)
Deviance Scaled Poisson	0.9704	1.1035 (0.0006)
Negative Binomial	0.9704	1.1282 (0.0029)

Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 13

Reviewer's Comments:

1. *Applicant's primary analysis based on all available data (N=735) inappropriately applied the alpha spending and was not in line with the recommended practice from the statistical and trial integrity perspectives. In the case where a decision is made to stop the trial at interim, the primary inference is recommended to be based on the data available at the interim analysis, using the pre-specified alpha level. As a result, the non-inferiority of Octafibrin compared with cryoprecipitate was demonstrated, but the superiority couldn't be supported due to the upper limit of the CI was above 1. The final updated analysis, using all available data, is recommended to be considered as supportive analysis.*

2. *As described above, more appropriate alpha should be used to assess the non-inferiority for all available data. I used two alphas; one is the pre-specified alpha in the interim analysis 0.00258. Another is treating the updated analysis as if it's another interim point of the analyses, the alpha spent for the updated analysis is 0.00508 based on information fraction 735/1200 using O'Brien-Fleming method. The updated analysis results based on these two alphas and alpha used by applicant are presented in Table 7. Non-inferiority was supported by the analyses using various alphas.*

Table 7: Updated Primary Efficacy Analysis Based on Different Alphas (Updated mITT, N=735)

	Estimate of mean ratio	***99.742% Upper CI*** [a]	***99.492% Upper CI*** [b]	***97.5% Upper CI*** [c]	***p-value***
Ordinary Poisson	*0.9569*	*1.0065*	*1.0024*	*0.9914*	*<0.0001*
Deviance scaled Poisson	*0.9569*	*1.1485*	*1.1317*	*1.0875*	*0.0003*
Negative Binomial	*0.9569*	*1.1859*	*1.1655*	*1.1121*	*0.0016*

[a] *Use pre-specified alpha of 0.00258 in the interim analysis*
[b] *Treat the updated analysis as if another interim point of the analyses with information fraction 735/1200, the alpha spent for the updated analysis is 0.0034.*
[c] *Alpha of 0.025 wad used by applicant in the updated analysis.*
Source: FDA statistical reviewer's analysis.

3. *The interim data and final data were found to be over-dispersed as the test results for the negative binomial dispersion parameter were significant. Thus, the equal mean and variance assumption in the ordinary Poisson regression was violated, the deviance scaled Poisson regression and Negative Binomial regression models were more appropriate and yielded more reliable conclusions.*

4. *In this study, the primary efficacy endpoint was the total number of units of ABPs administered during the 24 hours after termination of CPB. There are significant proportion of the ABP units included in the primary efficacy analysis were administered prior to the first IMP administration and therefore have no association with the treatment being evaluated in the study. Analysis using post-IMP ABP*

transfusions were conducted for the primary efficacy endpoint in the interim mITT (N=605) and updated mITT population (N=735).

In the interim analysis, the mean (SD) of ABP units administered following the first IMP administration to 24 hours after CPB end was 9.52 (15.15) for Octafibrin and 9.21 (15.73) for cryoprecipitate. In the updated analysis, the mean (SD) of ABP units was 8.65 (14.15) for Octafibrin and 8.92 (14.71) for cryoprecipitate. The non-inferiority was supported by results using ordinary Poisson regression in both interim and updated analyses. However, as the data was found to be over-dispersed, the statistically more appropriate models, deviance-scaled Poisson and Negative Binomial regression methods, indicated the non-inferiority no longer held in both analyses (Table 8). Thus, the non-inferiority conclusion for Octafibrin compared to cryoprecipitate in terms of the total ABP units administered following the first IMP administration to 24 hours after CPB end was not robust.

Table 8: Primary Efficacy Endpoint Analysis on the ABPs Given After IMP, up to 24 Hours After Termination of CPB (Interim mITT and Updated mITT)

Interim mITT (N=605)		
	Estimate of mean ratio	***99.742% Upper CI (p-value)***
Ordinary Poisson	*1.0335*	*1.1132 (<0.0001)*
Deviance Scaled Poisson	*1.0335*	*1.4005 (0.0846)*
Negative Binomial	*1.0335*	*1.5174 (0.1384)*
Updated mITT (N=735)		
	Estimate of mean ratio	***99.742% Upper CI (p-value)***
Ordinary Poisson	*0.9698*	*1.0397 (<0.0001)*
Deviance Scaled Poisson	*0.9698*	*1.2762 (0.0150)*
Negative Binomial	*0.9698*	*1.3703 (0.0424)*

Source: FDA statistical reviewer's analysis.

6.1.11.2 Analyses of Secondary Endpoints

The secondary endpoints below were analyzed in an exploratory manner, presenting summary statistics along with the presentation of two-sided 95% CIs or one-sided 97.5% CIs. There was no plan for multiplicity control in the analyses of secondary endpoints.

Transfusion of ABPs Within 7 Days After Surgery Start

In the updated mITT population (N=735), the means (SDs) of ABPs transfused in the FIBRGA group and cryoprecipitate group were 22.51 (24.41) and 22.30 (21.69), respectively, resulting in a ratio of 1.0093 (97.5% upper CI: 1.0406) using Poisson regression. Analysis results using deviance scaled Poisson regression and negative binomial regression, and in updated PP population analysis were comparable.

Transfusion of RBCs, Platelets and FFP Within 24 Hours after start of cardiac surgery

Total number of units of ABPs administered within 24 hours after start of cardiac surgery differentiated by RBCs, pooled and apheresis platelets and plasma were presented in Table 9. The updated PP analysis had similar results.

Table 9: Total Number of RBC, Platelet and FFP Units Used Within 24 Hours After Start of Cardiac Surgery (Updated mITT; N=735)

		Mean (SD)	Median (IQR)	Ratio Estimate (97.5% upper CI)*
RBCs	Octafibrin (N=372)	4.69 (5.55)	3.00 (1-7)	1.0511 (1.1247)
	Cryoprecipitate (N=363)	4.46 (5.11)	3.00 (1-6)	
Platelets	Octafibrin (N=372)	9.53 (8.63)	8.00 (4-12)	0.9543 (0.9995)
	Cryoprecipitate (N=363)	9.98 (8.49)	8.00 (4-12)	
Plasma	Octafibrin (N=372)	4.83 (6.94)	3.00 (0-6)	0.9913 (1.0586)
	Cryoprecipitate (N=363)	4.87 (5.87)	4.00 (0-6)	

* Ratio estimate and 97.5% upper CIs are calculated using ordinary Poisson regression
Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 14.2.2-13

Major Bleeding According to the UDPB During the First 24 Hours After Termination of CPB

The frequency distribution of bleeding categorized according to the UDPB is presented in Table 10. There were no notable differences in proportions of patients in each bleeding categories between the two groups. The PP analysis (N=725) had similar results.

Table 10: Frequency Distribution of Bleeding Categorized According to the UDPB During the First 24 Hours After Termination of CPB (Updated mITT; N=735)

	Octafibrin, N (%)	Cryoprecipitate, N (%)	Total, 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)

* 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.
Source: sBLA 125612/133; Clinical Study Report, Table 15

Restoration of Plasma Fibrinogen Level by Study Treatment: Effect of First Dose of IMP

Plasma fibrinogen level data is only shown for samples taken with 75 minutes before and after the start of the infusion. Table 10 summarizes the plasma fibrinogen level before and after first does of IMP. The fibrinogen level increased from 1.72 ± 0.65 g/L to 2.45 ±

0.59 g/L in the Octafibrin group and from 1.74 ± 0.58 g/L to 2.32 ± 0.58 g/L for the cryoprecipitate group. The mean increase in fibrinogen level in Octafibrin group and cryoprecipitate group were 0.85 ± 0.43 g/L and 0.69 ± 0.40 g/L, respectively, resulting a difference of 0.16 g/L with 95% CI of (0.06, 0.26). The Hodges-Lehmann estimator of the median difference in plasma fibrinogen levels between the two groups was 0.17 with 95% CI (0.07, 0.26).

Table 11: Plasma Fibrinogen Level Before and After First Dose of IMP (Updated mITT; N=735)

		N	Mean (SD)	Median (IQR)
Pre IMP	Octafibrin	223	1.72 (0.65)	1.60 (1.30-2.00)
	Cryoprecipitate	182	1.74 (0.58)	1.67 (1.34-2.00)
Post IMP	Octafibrin	253	2.45 (0.59)	2.41 (2.12-2.79)
	Cryoprecipitate	242	2.32 (0.58)	2.23 (1.97-2.54)
Post - Pre	Octafibrin	157	0.85 (0.43)	0.86 (0.60-1.09)
	Cryoprecipitate	120	0.69 (0.40)	0.68 (0.44-0.95)

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.
Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 16

6.1.11.3 Subpopulation Analyses

Subgroup analyses of the primary endpoint was conducted according to sex, age group, race, whether the patient was adjudicated to be in a critical state before surgery, whether the surgery was elective or non-elective and whether the surgery was complex or non-complex.

A critical state before surgery was defined as a patient who underwent emergency surgery and had any of the following conditions: ventricular tachycardia or fibrillation or cardiac arrest; preoperative cardiac massage; preoperative ventilation before anesthetic room; hemodynamic support requiring preoperative inotropes or ventricular assist devices; preoperative acute renal failure (anuria or oliguria <10 mL/hour); or acute aortic dissection.

Table 12 summarizes subgroup analyses results. The ABP units administered within 24 hours after CPB end were in general numerically similar across sex and age groups, except one patient with age <18 years. Note that because over 70% of the patients were White, the interpretation of the differences in the race groups may be limited. For both the Octafibrin and cryoprecipitate groups, the mean number of units of ABPs was much higher for the patients who were in a critical state before surgery, underwent non-elective surgery and underwent complex surgery compared to those not in these groups. The difference of estimated ratio between critical group and non-critical group was noteworthy. Additional post hoc analysis of efficacy endpoints adjusted for critical state before surgery was performed, and was presented in Section 6.1.11.5.

Table 12: Subgroup Analyses of Total Number of ABP Units Used Within 24 Hours After Termination of CPB (Updated mITT; N=735)

	N[a]	Octafibrin Mean (SD)	N[b]	Cryoprecipitate Mean (SD)	Ratio Estimate (97.5% Upper CI)[c]
Sex					
Female	113	14.73 (11.48)	105	14.00 (9.59)	1.0518 (1.1283)
Male	259	16.98 (18.50)	258	18.26 (17.90)	0.9297 (0.9688)
Age					
< 18 years	1	4.00	0	-	-
18 - 65 years	194	16.62 (18.69)	203	16.62 (17.54)	1.0005 (1.0500)
> 65 years	177	16.00 (14.29)	160	17.55 (13.98)	0.9117 (0.9605)
Race					
American Indian or Alaska Native	1	12.00	2	11.50 (0.71)	1.0435 (2.0970)
Asian	48	11.69 (11.93)	54	14.07 (11.49)	0.8304 (0.9262)
Black or African American	3	9.00 (1.00)	5	11.40 (9.37)	0.7895 (1.2480)
White	268	16.71 (16.78)	253	17.29 (17.19)	0.9660 (1.0071)
Other	52	18.92 (19.81)	49	19.71 (14.70)	0.9599 (1.0490)
State before surgery					
Critical	63	29.57 (21.51)	38	23.84 (14.39)	1.2403 (1.3428)
Non-critical	309	13.59 (14.12)	325	16.23 (16.07)	0.8370 (0.8717)
Surgery urgency status					
Elective	231	11.73 (11.82)	235	14.40 (13.69)	0.8145 (0.8567)
Non-elective	141	23.77 (20.47)	128	21.84 (18.79)	1.0880 (1.1440)
Complexity of surgery					
Complex	267	18.48 (17.65)	260	18.83 (17.54)	0.9813 (1.0209)
Non-complex	105	10.73 (12.46)	103	12.48 (10.22)	0.8603 (0.9320)

[a] Number of patients treated with Octafibrin in each subgroup.
[b] Number of patients treated with Cryoprecipitate in each subgroup.
[c] Ratio estimate and 97.5% upper CIs are calculated using ordinary Poisson regression.
Source: Adapted from sBLA 125612/133; Clinical Study Report, Table 14.2.1-9, 14.2.1-10, 14.2.1-17, 14.2.1-18, 14.2.1-25, 14.2.1-26, 14.2.4.1-1, 14.2.4.1-2, 14.2.4.2-1, 14.2.4.2-2, 14.2.4.3-1, 14.2.4.3-2, 14.2.4.4-1, 14.2.4.4-2, 14.2.4.5-1, 14.2.4.5-2, 14.2.4.6-1, 14.2.4.6-2

6.1.11.5 Exploratory and Post Hoc Analyses

A post hoc analysis of the primary efficacy endpoint adjusted for critical state before surgery for updated mITT (N=735) was performed by the applicant. The estimate of the ABP ratio was 0.9105 with 99.742% upper CI of 0.9580 using Poisson regression. I conducted the similar analysis for the interim mITT (N=605), where ABP ratio was 0.9320 with 99.742% upper CI of 0.9849. In addition, from Table 10 urgency and complexity of surgery also impacted the units of ABPs, results using Poisson regression with all three covariates were comparable.

6.1.12 Safety Analyses

The safety analysis focused on treatment-emergent adverse events (TEAEs), i.e., AEs that started or worsened after start of infusion with IMP.

6.1.12.1 Methods

The safety analysis was performed for the mITT population. Safety outcomes were analyzed analogously to the primary endpoint, with point estimates and two-sided 95% CIs being presented in addition to descriptive statistics.

6.1.12.3 Deaths

During the period from termination of CPB up to postoperative Day 28, 35 (9.41%) patients in the Octafibrin group and 27 (7.44%) patients in the cryoprecipitate group died. Table 13 summarizes the death in the updated mITT population.

Table 13: Summary of Timing of Deaths in the FIBRES Study (Updated mITT; N=69)

	Octafibrin (N=40)	**Cryoprecipitate (N=29)**
Death within 24 hours, N (%)	8 (20.00)	2 (6.90)
Death after 24 hours up to 48 hours, N (%)	2 (5.00)	4 (13.79)
Death after 48 hours up to 7 days, N (%)	12 (30.00)	10 (34.48)
Death after 7 days up to 28 days, N (%)	13 (32.50)	11 (37.93)
Death after 28 days, N (%)	5 (12.50)	2 (6.90)

Abbreviations: CPB = cardiopulmonary bypass; mITT = modified intention-to-treat; N = number of patients.
Source: sBLA 125612/133; Clinical Study Report, Table 28

6.1.12.4 Nonfatal Serious Adverse Events

In total, 1296 treatment-emergent adverse events occurred in 512 patients during the study: 623 events in 248 (66.7%) patients in the Octafibrin group, and 673 events in 264 (72.7%) patients in the cryoprecipitate group. In the Octafibrin group, 224 SAEs occurred in 117 (31.5%) patients; in the cryoprecipitate group, 264 SAEs occurred in 126 (34.7%) patients (Table 14).

Table 14: Summary of Treatment-Emergent Adverse Events (Updated mITT; N=735)

	Octafibrin (N=372)	**Cryoprecipitate (N=363)**
AE, n	623	673
Patients with AE, n (%)	248 (66.7)	264 (72.7)
Severity of AE, n		
Mild	249	227
Moderate	233	261
Severe	141	185
Probably or possibly related AE, n	0	0
SAE, n	224	264
Patients with SAE, n (%)	117 (31.5)	126 (34.7)
Death*, n (%)	35 (9.41)	27 (7.44)

* In period between termination of CPB and postoperative Day 28.
Abbreviations: AE = adverse event; CPB = cardiopulmonary bypass; mITT = modified intention-to-treat; n = number of AEs; N = number of patients; SAE = serious adverse event.
Source: sBLA 125612/133; Clinical Study Report, Table 26

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

FIBRES study was a phase 3, group sequential with one IA, non-inferiority study including subjects undergoing cardiac surgery with CPB in whom fibrinogen supplementation was ordered. The primary endpoint was the total number of ABP units used within 24 hours after termination of CPB. In the IA, a total of 605 treated patients were included with 302 in the Octafibrin group and 303 in the cryoprecipitate group. The means (SDs) of ABPs transfused in the Octafibrin group and cryoprecipitate group were 17.08 (17.69) and 17.39 (17.02), respectively, resulting in a ratio of 0.9822 using the ordinary Poisson regression. A one-sided hypothesis test with a type I error probability control at $\alpha_1 = 0.00258$ gave a 99.742% upper CI limit of 1.0375, below the 1.20 NI margin, demonstrating non-inferiority ($p<0.0001$). The study was stopped early due to this statistically significant efficacy result. In the updated analysis, 735 patients were included with 372 in the Octafibrin group and 363 in the cryoprecipitate group. The estimated ratio of ABPs was 0.9569 and the nominal 97.5% upper CI limits ranged from 0.9914 to 1.1121 across three statistical models. These results supported the non-inferiority conclusion but did not support the superiority conclusion as the upper bounds from the more appropriate models were above 1.0.

As for safety, of the 735 patients in the study, 224 SAEs occurred in 117 (31.5%) patients in the Octafibrin group and 264 SAEs occurred in 126 (34.7%) patients in the cryoprecipitate group. In the period from termination of CPB to postoperative Day 28, 35 (9.41%) patients in the Octafibrin group and 27 (7.44%) patients in the cryoprecipitate group died.

10.2 Conclusions and Recommendations

In conclusion, there were no major statistical issues related to the submission. Primary and secondary efficacy results have been verified. The FIBRES study data supported the non-inferiority of FIBRYGA compared to cryoprecipitate as fibrinogen supplementation in bleeding adult and pediatric patients with acquired fibrinogen deficiency. However, the data do not support a conclusion of superiority of FIBRYGA to cryoprecipitate in this indication. I defer to the clinical reviewer on the acceptance of the safety profile of FIBRYGA.