Summary Basis for Regulatory Action

Date	June 9, 2017
From	Ze Peng, PhD, Committee Chair
BLA #	STN 125612/0
Applicant Name	Octapharma Pharmazeutika Produktionsges m.b.H.
Date of Submission	June 9, 2016
Goal Date	June 9, 2017
Proprietary Name / Established name	FIBRYNA / Fibrinogen (Human)
Indication	For the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryna is not indicated for dysfibrinogenemia.
Recommended Action:	Approval
Signatory Authorities Action	**Wilson W. Bryan, MD** *Office Signatory Authority:* ☒*I concur with the summary review* ☐*I concur with the summary review and include a separate review to add further analysis* ☐*I do not concur with the summary review and include a separate review*

Discipline	Reviewer name
Clinical • *Clinical Studies* • *Postmarketing safety/epidemiological* • *Bioresearch Monitoring*	*Bindu George, MD (OTAT)* *Victor Baum, MD (OBRR)* *Faith Barash, MD, MPH (OBE)* *Anthony Hawkins, MS (OCBQ)* *Colonious King (OCBQ)*
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Devices	*Sapana Patel, PharmD (CDRH)* *Rakhi Dalal, PhD (CDRH)*
Advisory Committee (AC)	*Not presented at the Blood Products AC*

1. Introduction

Octapharma Pharmazeutika Produktionsges m.b.H. (Octapharma) submitted an original biologics license application (BLA) to seek U.S. licensure for Fibrinogen (Human). The product is a lyophilized powder in a crimp-sealed, stoppered, glass container, available in a dosage strength of approximately 1 g of human fibrinogen. The product is reconstituted with sterile Water for Injection (sWFI, not provided), for intravenous administration. The proprietary name of the product is FIBRYNA.

FIBRYNA is a human fibrinogen concentrate indicated for the treatment of acute bleeding episodes in adults and adolescents with congenital fibrinogen deficiency (CFD), including afibrinogenemia and hypofibrinogenemia. FIBRYNA is not indicated for treatment of dysfibrinogenemia (dysfunctional fibrinogen).

This document summarizes the basis for approval for FIBRYNA and highlights key review issues. The review team recommends approval of this BLA with a postmarketing required study to further characterize the potential for thrombotic risks associated with treatment of major bleeding episodes at doses targeted to achieve fibrinogen levels of 150mg/dL.

2. Background

FIBRYNA is a sterile, purified, virus-inactivated, and nanofiltered (20 nm) fibrinogen concentrate, manufactured at Octapharma's facility at Oberlaaer Strasse 235, A-1100 Vienna, Austria. It is produced from pooled U.S. human (b) (4) Plasma by using (b) (4) , and filtration steps. During the manufacturing process of FIBRYNA, significant viral reduction is obtained via a combination of two dedicated virus inactivation/removal steps: solvent/detergent (S/D) treatment and nanofiltration (20 nm). FIBRYNA has not been approved outside of the U.S. There is another human fibrinogen product licensed in the U.S. for the treatment of CFD – RiaSTAP®, manufactured by CSL Behring (CSLB). FIBRYNA will be the second product available in the U.S. for the treatment of bleeding episodes in adults and adolescents with CFD, including afibrinogenemia and hypofibrinogenemia.

Disease Background

Fibrinogen, or Factor (F) I in the human coagulation cascade, is a glycoprotein that in the presence of thrombin forms insoluble fibrin strands which are then cross linked by FXIII to form a clot. The three genes (i.e., Bβ (FGB), Aα (FGA), and γ (FGG)) coding for fibrinogen are responsible for the production of Aα, Bβ and γ-polypeptides, which polymerize to form insoluble fibrin. The normal fibrinogen level, measured by the Clauss method, ranges from 150 - 350 mg/dL. Normal fibrinogen has a half-life of 3-5 days. Uncontrolled hemorrhage is more likely to occur at critical plasma fibrinogen levels that fall below the range of 50-100 mg/dL. In cases of major surgical intervention, precise monitoring of fibrinogen levels is essential to adjust the dosing of replacement therapy to prevent re-bleeding or post operative bleeding.

CFD is an autosomal recessive disease which includes a group of rare disorders, including afibrinogenemia (complete absence or extremely low levels of plasma fibrinogen), hypofibrinogenemia (reduced fibrinogen concentration to ≤ 150 mg/dL), dysfibrinogenemia (dysfunctional fibrinogen), and hypodysfibrinogenemia (both reduced quantity and quality of fibrinogen). The estimated prevalence of afibrinogenemia is approximately 1:1,000,000, although the prevalence increases in areas of increased consanguinity.

Afibrinogenemia manifests clinically as a highly variable bleeding dyscrasia. Bleeding occurs in 78% of patients with afibrinogenemia, with 10% of the bleeding events being intracranial hemorrhages (ICH), which are a major cause of death in patients with afibrinogenemia. Neonatal bleeding (e.g., bleeding from the cord stump) is the presenting event in a majority of patients. Other affected organs are skin, gastrointestinal tract, genitourinary tract, and central nervous system. Menometrorrhagia can occur, and first-trimester abortions can occur in afibrinogenemic women, with a 17% incidence of recurrent spontaneous abortions. The frequency of bleeding episodes (BEs) varies from none to multiple episodes per year. The reported frequency of BEs is 0.7 per year. The symptoms of hypofibrinogenemia are usually milder. These subjects can be asymptomatic, but are at risk of excessive bleeding with trauma.

Congenital afibrinogenemia is associated with a high risk arterial or venous thrombosis, which can occur even in the absence of fibrinogen replacement therapy (FRT). In a retrospective study of 55 patients with afibrinogenemia, the spontaneous rate of thrombosis was 4%, including one case of arterial thrombosis and one case of sagittal sinus thrombosis.

Treatment of CFD

Management of CFD consists of on-demand treatment of acute bleeding with FRT, along with peri-operative management with FRT. Prophylaxis is occasionally used during pregnancy (to prevent miscarriage or post-partum hemorrhage), and following a life-threatening BE such as ICH. FRT is based on achieving target levels of fibrinogen, and is the mainstay of treatment of acute bleeding events, perioperative management, and in special situations for routine prophylaxis.

Although fibrinogen concentrate (FC) products were approved in the U.S. for treatment of CFD, the marketing licenses were revoked in 1977 due to risks of hepatitis infection and suspected lack of effectiveness. After improvements in safety and purity, Haemocomplettan® manufactured by CSLB has been approved in some countries since 1985. In the U.S., a human fibrinogen concentrate (RiaSTAP®), manufactured by CSLB from pooled plasma, was approved via the Accelerated Approval pathway in 2009, for the treatment of acute BEs in patients with afibrinogenemia and congenital hypofibrinogenemia.

FRT and dosing of fibrinogen are primarily based on the Guideline issued in 2004 by the United Kingdom Haemophilia Center Doctors' Organization. The Guideline was developed based on the collective clinical experience and published literature. The guideline recommends 1) FC as the treatment of choice, 2) target levels of fibrinogen of 100 mg/dL to treat major spontaneous bleeding and pre-operatively with laboratory monitoring for repeat infusions until hemostasis is achieved, and target levels of 50 mg/dL until wound healing is complete, and 3) secondary prophylaxis following life-threatening bleeding to minimize the risk of re-bleeding, with target trough levels of 50 mg/dL.

Thrombotic risks associated with available therapies for FRT

The most notable risks from FRT in patients with CFD, especially those with congenital afibrinogenemia, relate to thrombosis, hypersensitivity reactions, development of anti-fibrinogen antibodies, and transmissible infectious agents.

CFD is a rare bleeding disorder with paradoxical risks of spontaneous arterial and venous thrombosis of approximately 4%, particularly in patients with congenital afibrinogenemia. FRT may increase the risk of venous thrombotic events; therefore, FRT should be used with caution.

The FIBRYNA target dose of 150 mg/dL for the treatment of major bleeding episodes is higher than the target plasma fibrinogen level recommended by the United Kingdom Guideline. It is unclear whether a dose-dependent effect on thrombotic risks exists. However, higher target levels could result in longer exposures to FRT, and therefore increase the thrombotic risks.

Safety

The safety data from the FORMA-01 and FORMA-02 studies do not raise substantial concerns following single-dose administration in patients with congenital fibrinogen deficiency. The available data are limited due to the small sample size of the clinical safety dataset. There is also a long history of safe use with other fibrinogen concentrates. However, the literature suggests that there may be paradoxical thrombotic events in afibrinogenemic patients. For this reason, the review team recommends that the safety profile of FIBRYNA be further characterized after marketing approval.

Regulatory Milestones for STN 125612/0

This BLA was received on June 9, 2016. This product is classified as a biological product/device combination product. As such, CBER consulted the Center for Devices and Radiological Health (CDRH) for the evaluation of the reconstitution device set (Octajet and the particle filter), as well as a human factors study. All identified issues were adequately resolved in the course of the review. Thus, the review team determined that the applicant has satisfactorily addressed all major issues, and recommends approval of the original BLA for FIBRYNA.

This original BLA was reviewed under the PDUFA V program (Standard 12 Month). The BLA review milestones are listed below.

Milestone	Date
Received	June 9, 2016
Filing date	August 5, 2016
Inspection of Vienna facility	Waived
Mid-cycle communication	December 12, 2016
Late-cycle meeting	March 15, 2017
Action Due	June 9, 2017

3. Clinical / Statistical / Pharmacovigilance

a) Clinical Program

The clinical studies to support STN 125612/0 for FIBRYNA were performed under IND 14777. The proposed indications are for the treatment of acute bleeding episodes (BEs) in adults and adolescents (≥ 12 years) with CFD.

Two studies, FORMA-01 and FORMA-02, were conducted to support the efficacy and safety of FIBRYNA in the treatment of acute BEs. FORMA-01 was a Phase 2 crossover pharmacokinetic (PK) and efficacy study in 22 subjects ≥12 years old in the non-bleeding state. FORMA-02 was an uncontrolled Phase 3 primarily efficacy and safety study of FIBRYNA for the treatment of acute bleeding (major and minor BEs) and perioperative management of bleeding for major and minor surgery.

- IND submission: July 22, 2011
- IND teleconference: August 24, 2011
    - FDA informed the sponsor that an unmet need does not exist since the approval of RiaSTAP®, and therefore the Accelerated Approval pathway is not available for Octafibrin (former name for FIBRYNA).
    - FDA requested that the BLA include efficacy data for ≥10 subjects.

- FDA comments on the FORMA-02 study: November 23, 2013

  - The primary efficacy endpoint should be based on assessment of hemostatic efficacy for the first bleeding episode.

  - An objective measure for restoration of hemostasis was requested.

- FDA advice/information request letter: April 14, 2016

  - The final efficacy assessment by the Independent Endpoint Adjudication Committee (IDMEAC) should be the assessment used for the primary efficacy analysis.

- Pre-BLA meeting: April 22, 2016

Clinical Studies

- FORMA-01 enrolled 16 adults and six adolescents ages 12 - 65 years with congenital afibrinogenemia. The primary objective of FORMA-01 was to compare the PK and PD parameters of FIBRYNA to the U.S. licensed fibrinogen concentrate product, in subjects with congenital afibrinogenemia in the non-bleeding state. The interpretation of the efficacy results, based on PK and PD parameters, is discussed in the Clinical Pharmacology section. The secondary objective of FORMA-01 was to assess the safety of a single dose of FIBRYNA 70 mg/kg. There were no deaths, no thrombotic events, hypersensitivity reactions, or immune-related adverse events (AEs) in this study. There were no serious AEs (SAEs) related to FIBRYNA.

- FORMA-02 is an ongoing, single-arm Phase 3 efficacy study of FIBRYNA for on-demand treatment of BEs and for perioperative prophylaxis in patients ≥12 years old (range 13 - 53 years). This study is projected to conclude in Q3 2020. Subjects were to be dosed to target plasma levels of fibrinogen, using the (b) (4) assay, of 100 mg/dL for the treatment of minor bleeding or minor surgery, and 150 mg/dL for the treatment of major bleeding or pre-operatively and intra-operatively during surgery. The study protocol specifies definitions of minor and major bleeding, as well as minor and major surgery. Data from 11 adults and two adolescents are available for review through the planned interim analysis.

  Efficacy outcomes were assessed on four-point scales for treatment of BEs and perioperative bleeding. A treatment success was defined as a hemostatic efficacy rating of excellent or good at 24 hours following administration of FIBRYNA for the treatment of acute bleeding, or following completion of surgery for perioperative management. The primary efficacy endpoint for acute bleeding was the proportion of subjects with a treatment success for treated first BEs, or during the perioperative period for any surgery, as assessed by the Independent Data Monitoring and Endpoint Adjudication Committee (IDMEAC). The pre-specified criterion for study success was defined by the lower bound of the two-sided 90% Blyth-Still-Casella confidence interval (CI) for the proportion of successes to be ≥0.70. The secondary efficacy endpoint was based on outcomes of all BEs.

- Data from 13 subjects were submitted for analysis. However, only 11 subjects were treated for acute bleeds, and only 10 subjects were evaluable for the first BE. All subjects achieved hemostatic control with a single dose of FIBRYNA. The hemostatic efficacy for the primary efficacy evaluable population of 10 subjects was 100% with the lower bound of 90% CI at 0.78. The study thus met the protocol-defined success criterion.

- None of the BEs were major. The data to support the efficacy of FIBRYNA in major bleeding are based on documentation of successful hemostasis a) in subjects who achieved target fibrinogen levels of >140 mg/dL following treatment of six BEs, and b) in the single subject who underwent major surgery who achieved target plasma fibrinogen levels of 220 mg/dL. These data are sufficient to support approval of FIBRYNA for the treatment of major bleeding in this rare disorder. Additionally, the published data support control of bleeding at lower plasma fibrinogen levels of 100mg/dL.

- Of the 23 BEs treated with FIBRYNA in FORMA-02, 22 were evaluable for hemostatic efficacy. All BEs were minor. For one of the 22 evaluable BEs, there was missing efficacy information; therefore, the clinical reviewer assessed the outcome as a treatment failure for the secondary efficacy analysis. For the remaining twenty-one evaluable BEs in 13 subjects, outcomes were assessed as successful. Therefore, the hemostatic efficacy rate was 95% with the 90% lower bound of the CI at 0.80. Thus, the results of the secondary efficacy analysis are supportive of the primary efficacy findings.

- Surgical prophylaxis was assessed for four surgical procedures in four subjects; three procedures were classified as minor and one was classified as major. Hemostasis in all four of these surgeries was rated as excellent or good by the IDMEAC, so the overall success rate was 100%.

- (b) (4)

- FORMA-02 provide the primary safety data for this BLA with the FORMA-01 data being supportive of FORMA-02.

- There were no thrombotic events or development of antibodies to FIBRYNA in both studies. In FORMA-02, one subject developed mild hypersensitivity reactions manifested as rash and pruritis requiring corticosteroid and anti-histamine treatment. For subsequent treatments with FIBRYNA, this subject required pre-treatment with anti-histamine and corticosteroids. No deaths or study discontinuation due to AEs occurred in either study.

- The Applicant proposes to dose subjects to target plasma fibrinogen levels of 150mg/dL for the treatment of major bleeding. This target level is higher than the proposed target level for minor bleeding. The safety data from FORMA-02 are currently limited to treatment of minor bleeding.

To assess the safety of the dose targeted to achieve a plasma fibrinogen level of 150 mg/dL, FORMA-02 safety data for treatment of minor BEs that resulted in target plasma fibrinogen level >140 mg/dL were evaluated. Six of the 22 BEs and one treatment for surgical prophylaxis (post-infusion plasma fibrinogen level of 220 mg/dL) were evaluated. None of seven treatments were associated with serious risks; i.e., there were no discontinuations resulting from adverse events, thrombotic events, or deaths. However, the subjects received a single infusion of FIBRYNA, and not multiple doses as might be anticipated with major bleeding. In addition, the target population of major bleeding was not specifically evaluated. Therefore, the generalizability of these safety data is unclear.

Conclusion: The efficacy and safety data are adequate to support marketing approval for the treatment of minor and major bleeding in adults and adolescents.

FORMA-02 and FORMA-01 are limited with regard to the safety data a) for the dose proposed to treat major bleeding b) to support multiple administrations as may be required for the treatment of acute major bleeding and for the perioperative management of bleeding. As noted previously, subjects with CFD, particularly subjects with congenital afbrinogenemia, are at risk for paradoxical arterial and venous thrombosis. In addition, based on the published literature, FRT has been associated with thrombotic risks, hypersensitivity reactions, and immunogenicity issues. Due to the limitations of the BLA safety data, and the known risks from the published literature, the review team recommends a required post-marketing study to further characterize the thrombotic risks of FIBRYNA.

- FORMA-04 is an ongoing trial to evaluate the efficacy and safety of FIBRYNA in children <12 years of age with congenital fibrinogen deficiency. No data from this study have been submitted in this BLA. This study plans to enroll ≥6 subjects with at least 3 subjects <6 years of age and at least 3 subjects 6-12 years of age. The trial design is similar to FORMA-02 and will additionally include a single PK analysis after enrollment. As of the BLA submission date three subjects have been enrolled in the trial. The anticipated completion date for this study is December 31, 2020.

Pharmacovigilance

Important identified risks of FIBRYNA include hypersensitivity reactions and thromboembolic events. As discussed above, a post-marketing safety study will be required. FDA recommends the following for postmarketing safety monitoring:

1) Routine pharmacovigilance, including adverse event reporting under 21 CFR 600.80

2) Postmarketing Requirement (PMR) Under Section 505(o): Conduct a prospective observational study of patients ≥ 12 years of age with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYNA for at least 10 major BEs to further characterize the risk of thromboembolic events following FIBRYNA use.

Study timeline (proposed by the Applicant):

Final Protocol Submission: September 30, 2017
Study Completion Date: March 31, 2024
Final Report Submission: June 30, 2024

To fulfill this PMR, the Applicant has proposed a prospective multicenter, observational, one-arm study:

- Primary Objective: characterize thromboembolic event (TEE) incidence in on-demand FIBRYNA treatment of major bleeding

- Minimum number of acute major BEs: 10

- Sample size estimation to assess safety of the treatment of at least 10 major BEs over 6 years: 25 patients with congenital afibrinogenemia or hypofibrinogenemia

  During a study duration of 6 years, about 105 bleeding episodes might be expected, including 10 major BEs. As a contingency plan, the sponsor has proposed to extend the study duration beyond the planned six years if the target minimum number of 10 BEs is not met.

- Follow-up: All BEs will be followed for up to 28 days after treatment. Hospitalized patients will receive daily assessments. In the outpatient setting, patients will be contacted by a study nurse in a telephone interview at 1week and 4 weeks after treatment.

Upon receipt of the final protocol, the FDA will evaluate the statistical analysis plan, information to be collected at baseline, frequency and methods for follow-up data collection, and information to be collected in follow-up.

Statistical Summary

The statistical review of the pivotal study, FORMA-02, basically concurs with the clinical review. The hemostatic efficacy analysis, conducted on the pre-specified data set comprised of 11 subjects, met the success criterion. Per the clinical review, there were 10 clinically evaluable subjects, and the success criterion was also met with this data set.

Post-Marketing Requirements

Please refer to the discussion of the safety data for the rationale for a required post-marketing study regarding treatment of acute major bleeding. The recommendations for post-marketing actions include:

- Post-marketing study to evaluate the risks of thromboembolic events, hypersensitivity reactions, and immunogenicity (development of anti-fibrinogen antibodies) from FIBRYNA in adults and adolescent subjects for the treatment of major bleeding.

- A post marketing required study under Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of FIBRYNA for the treatment of acute bleeding in children < 12 years of age with congenital afibrinogenemia and hypofibrinogenemia.

Bioresearch Monitoring

The Bioresearch Monitoring (BIMO) inspections were completed at two foreign clinical study sites conducting studies FORMA-01 and FORMA-02 for 12 subjects. A review of the Establishment Inspection Reports (EIRs) did not reveal problems that impact the data submitted in this BLA.

b) Pediatrics

FORMA-04 is an ongoing pediatric study in children <12 years of age to evaluate the efficacy and safety of FIBRYNA for a) the treatment of acute bleeding and b) (b) (4) . Pending submission of an initial Pediatric Study Plan (iPSP), FDA will grant a deferral request for the portion of the FORMA-04 study intended to evaluate the efficacy and safety of FIBRYNA for the treatment of acute bleeding. The planned study completion date is December 31, 2020. The draft pediatric plan for the deferral of FORMA-04 was discussed at the FDA's Pediatric Review Committee (PeRC) on February 16, 2017. There were no PeRC recommendations to modify FORMA-04 to satisfy PREA requirements.

There are sufficient efficacy and safety data to approve FIBRYNA for the treatment of acute bleeding for children ≥12 years of age. The study plan for the FORMA-04 study satisfies the PREA requirements and includes all age groups and covers the indication that is being approved for adults and adolescents. However, an iPSP is yet to be submitted for review by the PeRC.

c) Other Special Populations

When data were analyzed by age, sex or race, there were no significant differences in efficacy or safety profiles. However, no subject >53 years old has been enrolled in a clinical trial of FIBRYNA.

4. Chemistry, Manufacturing and Controls (CMC)

a) Product Quality

Description

FIBRYNA is a human plasma-derived, sterile, purified, virus inactivated and nanofiltered (20 nm) fibrinogen concentrate, supplied as a lyophilized powder for reconstitution with sWFI for intravenous injection. The product contains the following excipients and stabilizers: sodium chloride, sodium citrate dihydrate, glycine, and L-arginine hydrochloride. FIBRYNA is supplied in single-use containers having approximately 1 g Fibrinogen per container. Each container is labeled with the actual amount of Fibrinogen in grams determined using the (b) (4) assay. For this assay, no reference standard is required, which is consistent with the procedure

described in the (b) (4) . As an additional control, the amount of FIBRYNA is also measured using a (b) (4) assay, using an in-house reference standard calibrated against the (b) (4) for Fibrinogen in plasma, human ((b) (4)).

Summary of Manufacturing Process

Starting from pools of human U.S. (b) (4) Plasma to the final drug product, FIBRYNA is manufactured at Octapharma's facility at Oberlaaer Strasse 235, A-1100 Vienna, Austria.

(b) (4)

(b) (4)

(b) (4) filled in final containers in a nominal volume of 50 mL. The final containers are partially stoppered, and the product is lyophilized. After the completion of lyophilization, the final containers are fully stoppered and then capped, tested for the presence of (b) (4), subjected to visual inspection, labeled, and packaged.

Source material quality and control

FIBRYNA is manufactured from human (b) (4) Plasma obtained from FDA-approved U.S. plasmapheresis centers. The plasma donations used for FIBRYNA are tested, and found to be negative using serological assays for hepatitis B surface antigen (HBsAg), and antibodies against

Human Immunodeficiency Virus (HIV) – 1/2 and Hepatitis C Virus (HCV). The plasma donations are tested in "mini-pools" with Nucleic Acid Testings (NAT) for Hepatitis B Virus (HBV), HCV, Hepatitis A Virus (HAV) and HIV-1 and found to be negative. The plasma donations are also tested by NAT for human parvovirus B19 (B19V) DNA to exclude high-titer B19V donations, to ensure that the limit of B19V DNA in each mini-pool ((b) (4)) does not exceed 10^3 IU per mL.

In addition, in-process controls are performed on the manufacturing pool. (b) (4)

All other source materials used for FIBRYNA manufacture are qualified according to the monographs of the United States Pharmacopoeia (*USP*), National Formulary, or *Ph. Eur*., and do not contain animal- or human-derived materials that could potentially introduce contamination with adventitious agents. All these source materials are purchased from the approved suppliers and released against the approved specifications.

Critical process parameters and their control

Critical process parameters (CPPs) for the manufacturing process and their acceptable ranges were initially determined during process development. The acceptance ranges were further verified and adjusted during the optimization of the process steps and production of full-scale GMP batches. Operating parameters for each unit operation in the FIBRYNA process were examined for criticality prior to the execution of the conformance campaigns. These CPPs and their acceptance criteria have been justified.

Process validation

The manufacturing process of FIBRYNA was qualified through the production of (b) (4) consecutive conformance batches ((b) (4)), covering minimum and maximum process time. The results of in-process control and quality control testing for all the conformance batches complied with prospectively defined acceptance criteria, demonstrating that process validation was successful.

Specification for final drug product

The following release specifications are considered adequate to confirm product quality and manufacturing consistency.

Product quality attribute	Specification	Justification
Characters	A white or pale yellow, hygroscopic powder or friable solid	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Solubility	The preparation dissolved within (b) (4) minutes at 20 – 25°C; the	(b) (4)

	reconstituted solution is almost colorless and slightly opalescent	
Stability of solution	(b) (4)	(b) (4)
Water	(b) (4)	(b) (4)
Sterility	No growth or no growth detected	(b) (4)
Endotoxin	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4).
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	
Fibrinogen	(b) (4)	(b) (4)
Glycine	(b) (4)	(b) (4)
Citrate	(b) (4)	(b) (4)
Chloride	(b) (4)	(b) (4)
L-Arginine HCl	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Analytical methods for product quality

Suitable analytical methods have been validated to support quality control testing throughout manufacture, final product release, and stability monitoring. Clarifications were obtained through requests of additional documentation. All identified issues were adequately resolved in the course of the review through requests for supplemental data, or method re-validation.

Impurities

The impurity profile of FIBRYNA FDP is described in Report No. *020STD34x.312/00*. The product-related impurities include (b) (4) . These impurities were found either in detectable but small amounts or below the detection limits of the assays in the final drug product. The process-related impurities include (b) (4) . Again, these impurities were found either in detectable but small amounts or below the detection limits of the assays in the FIBRYNA FDP.

Container closure system

The primary packaging for Fibrinogen includes 100mL (b) (4) (glass (b) (4) vials supplied by (b) (4), 32mm brownish red (b) (4) rubber ((b) (4)) stoppers with Grade (b) (4) supplied by (b) (4), and 32mm Flip-Off Caps consisting of a white propylene cap, and a (b) (4) aluminum flip-top over-cover supplied by (b) (4). Octapharma conducted the container closure integrity testing at the OPG Vienna facility, employing the (b) (4) test method (using (b) (4)). They also performed (b) (4) testing of 100% of the final containers during the Visual Inspection process (at least (b) (4) hours post-crimping). All acceptance criteria were met.

Combination product

The FIBRYNA product kit contains two separate components, a lyophilized powder of Fibrinogen (Human) in a product container, and a reconstitution device set (i.e., Octajet and a particle filter ((b) (4))). Therefore, we consider this to be a combination product. CBER consulted with Drs. Sapana Patel and Rakhi M. Dalal from CDRH for evaluation of the relevant medical devices used in this combination product, and for evaluation of the human factors study.

The particle filter ((b) (4)) manufactured by (b) (4) is used for the reduction of particles during the reconstitution of the drug product. It has been cleared under 510(k) No. (b) (4) . Octajet, a single disposable transfer device is manufactured by (b) (4) . The data to support this device to be used for the reconstitution of FIBRYNA are summarized as follows:

- Octajet is composed of standard and common (b) (4) used in patient-contacting medical devices, which meet the requirements of USP Plastic Class VI, ISO 10993 and the requirements described in USP for physicochemical testing. The construction materials of Octajet are comparable to those commonly used in the manufacture of other disposable, single-use, sterile 510(k)-cleared medical devices, e.g., catheters.

- The total contact time between the Octajet materials and the FIBRYNA FDP which is eventually provided to the patients is within 1 minute, whereas those sterile 510(k)-cleared medical devices, e.g., catheters, have direct and longer-term contact with the patients.

- The risk assessment on the transient contact of Octajet with FIBRYNA was evaluated in the extractables studies according to the requirements of *Ph. Eur. 01/2009*. The test results showed that no hazardous materials were detected from Octajet during use. Moreover, the device is pharmaceutical grade and therefore has been demonstrated to have a specified level of impurities. Also, Octajet contains acceptable levels of bacterial endotoxins.

- The functionality testing data on Octajet appear to be sufficient.

- Octapharma performed two comparability studies, in which they demonstrated that the use of this reconstitution device set does not have significantly adverse impact on the quality of FIBRYNA FDP.

- The intended users of Octajet are health care professionals or physicians, and this device is a low risk device from a usability perspective as indicated in the human factor studies.

- Octajet has been cleared in Canada and the European Union.

Stability studies

The available stability data indicated no critical trends during the observed long-term storage period. Stability data submitted to this BLA supported the proposed shelf-life of FIBRYNA of 30

months when stored at 2°C - 25°C. The product solution must be used within 4 hours after reconstitution.

Evaluation of safety of product regarding adventitious agents

Production processes are controlled and monitored by specified process control parameters. Production processes have been investigated and validated concerning their ability to reduce microbes and prions.

Residual microbes are reduced by in-process filtration steps and removed by the validated (b) (4) final bulk solution. Thereafter, aseptic filling is performed and the product is freeze-dried. The final release tests include those for sterility and endotoxin.

To minimize the risk of transmissible spongiform encephalopathy (TSE) agent transmission, donors who are potentially at risk are excluded from plasma donation as specified in the current FDA guidance regarding donations collected in the U.S. Furthermore, the manufacturing steps including (b) (4) , and nanofiltration may contribute to the removal of potential TSE agent contamination.

As stated above, all plasma donations, minipools and manufacturing pools, are tested for viral markers in compliance with the requirements of FDA.

Additionally, the potential of viral contamination of FIBRYNA is mitigated by two dedicated viral clearance steps: S/D treatment ((b) (4)) at (b) (4) , and 20 nm nanofiltration (Planova 20N or Pegasus SV4). Octapharma has evaluated these steps in down-scale studies. The enveloped viruses selected in the studies include HIV-1; Pseudorabies virus (PRV, model for enveloped DNA viruses including HBV); and Bovine viral diarrhea virus (BVDV, model virus for enveloped RNA viruses). The non-enveloped viruses selected in the studies include HAV; and Porcine parvovirus (PPV, model virus for B19V). These viruses resemble viruses which may contaminate the production of FIBRYNA, and represent a wide range of physico-chemical properties in the testing of the ability of the manufacturing process to eliminate viruses. Down-scale studies on the relevant steps resulted in at least the following total log reduction factors, in parenthesis, for these viruses: (b) (4) . These results are sufficient to support the effectiveness of viral clearance in the commercial manufacturing process.

Total virus reduction factors (log_{10}) for inactivation/removal of various viruses achieved by the FIBRYNA manufacturing process

Manufacturing step	**Virus reduction factor (log_{10})**				
	Enveloped viruses			Non-enveloped viruses	
	HIV-1	PRV	BVDV	HAV	PPV
S/D treatment	≥ 5.2	≥ 6.6	≥ 5.8	Not done	Not done
Planova 20N nanofiltration	≥ 4.2	≥ 6.6	≥ 4.9	≥ 5.2	5.3

Total log reduction factors (S/D treatment + Planova 20N nanofiltration)	≥ 9.3	≥ 13.2	≥ 10.7	≥ 5.2	5.3
S/D treatment	≥ 5.2	≥ 6.6	≥ 5.8	Not done	Not done
Pegasus SV4 nanofiltration	≥ 3.9	≥ 6.3	≥ 5.0	≥ 5.2	4.5
Total log reduction factors (S/D treatment + Pegasus SV4 nanofiltration)	≥ 9.0	≥ 12.9	≥ 10.8	≥ 5.2	4.5

b) CBER Lot Release

The lot release protocol template was submitted to CBER for review and found to be acceptable after revisions. Samples were submitted to CBER in support of the BLA, tested by CBER and found to be acceptable. For routine lot release, the applicant will submit final container samples together with lot release protocols. A lot release testing plan was developed by CBER and will be used for routine lot release.

c) Facilities review/inspection

Facility information and data provided in the BLA for the manufacturing of Fibrinogen drug product were reviewed by CBER and found to be sufficient and acceptable.

The facility involved in the manufacture of Fibrinogen is listed in the table below. The activities performed and inspectional histories are noted in the table and further described in the paragraphs that follow.

Manufacturing Facilities Table for Fibrinogen

Name/address	FEI number	DUNS number	Inspection/ waiver	Results/ Justification
Drug Substance Manufacturing *Drug Product Manufacturing* *Drug Product Labeling* *Release Testing* Octapharma Pharmazeutika Produktions GmbH Oberlaaer Strasse 235, A-1100 Vienna, Austria	3002809097	301119178	Waived	Team Biologics February 26 to March 5, 2015 Voluntary Action Indicated (VAI) Team Biologics January 9-17, 2017 VAI

The Pre-license inspection was waived based on the results of Team Biologics surveillance inspection of the Octapharma OPG Vienna facility from February 26 to March 5, 2015, where the inspection was classified as VAI. No compliance issues were identified; all inspectional 483 observations were resolved.

Furthermore, the most recent Team Biologics surveillance inspection of the Octapharma OPG Vienna facility from January 9-17, 2017, was also classified as VAI.

d) Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31c. The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances, and no extraordinary circumstances exist that would require an environmental assessment.

Recommendation:

The manufacturing process for FIBRYNA is considered validated at the commercial scale and is sufficiently controlled to assure consistent manufacture of commercial product meeting acceptable release specifications. The reviewers from the Division of Plasma Protein Therapeutics, the Division of Manufacturing and Product Quality, and the Division of Biological Standards and Quality Control conclude that Octapharma has provided sufficient data and information on chemistry, manufacturing and controls to support the licensure of FIBRYNA.

5. Non-clinical Pharmacology/Toxicology

The nonclinical program for FIBRYNA consisted of pharmacodynamic, safety pharmacology, pharmacokinetic (PK), and toxicology studies in healthy animals and in animal models of disease. Intravenous administration of FIBRYNA in a sublethal disseminated intravascular coagulation (DIC) model partially restored the deficient fibrinogen (FIB) levels, partially corrected the prolonged levels of thrombin time (TT), and increased clot firmness as compared to the saline control. These improvements were in a dose-dependent manner and were similar to the results seen with an approved comparator product.

In safety pharmacology studies in healthy dogs, FIBRYNA was well-tolerated without any product-related adverse effects. In additional safety pharmacology studies in rabbits, FIBRYNA was not thrombogenic. Acute systemic toxicity studies in healthy mice and rats did not identify any adverse findings following administration of FIBRYNA. Local tolerance studies conducted in rabbits revealed acceptable levels of erythema at the FIBRYNA injection site.

No animal studies were conducted to evaluate potential carcinogenicity, *in vivo* mutagenicity, reproductive toxicity, or teratogenicity of FIBRYNA. No studies were conducted to determine if FIBRYNA could impair fertility. As FIBRYNA is a plasma-derived human protein, healthy, immune-competent animals receiving repeated doses of the product developed antibodies against coagulation factor X. Therefore, long-term, repeat-dose toxicity studies, as well as the standard carcinogenicity bioassay, were not feasible to conduct.

6. Clinical Pharmacology

A single clinical pharmacology study (FORMA-1) was conducted to evaluate the pharmacokinetic and pharmacodynamics following treatment with FIBRYNA.

This was a multinational, multicenter, prospective, randomized, controlled, crossover Phase 2 PK study in 22 patients with congenital fibrinogen deficiency. PK of FIBRYNA and Haemocomplettan® P/RiaSTAP® was determined in a crossover design. The reference therapy in this study was Haemocomplettan® P/RiaSTAP®, which is a marketed fibrinogen concentrate. The eligible patients were ≥12 years of age and had CFD (afibrinogenaemia) (plasma fibrinogen activity and antigen at screening below detection limit (<20 mg/dL)). There were 6 subjects between 12 and 18 years of age and 16 subjects >18 years of age (18-53 years). There were 7 males and 15 females in the study. There were 14 Caucasians and 8 Asians in the study.

This study consisted of two periods. Each study period lasted 45 days. Patients were randomized to receive a single infusion of either FIBRYNA or Haemocomplettan® P/RiaSTAP® in each of the two study periods. FIBRYNA was administered at a dose of 70 mg/kg body weight (based on the labeled potency) as an intravenous bolus injection at a maximum rate of 5 mL/min.

Blood samples for PK analyses were taken at the following time points: at baseline, 0.5, 1, 2, 4, 8, 24, 48, 96, 144, 216 and 312 hours post-infusion. Fibrinogen activity for PK analysis was measured by validated (b) (4) assay.

Maximum clot firmness (MCF) was assessed as a surrogate marker of efficacy (thromboelastography) using rotational thromboelastometry at baseline and 1 hour after administration of FIBRYNA or haemocomplettan. Both treatments resulted in significant increases from baseline in MCF.

Conclusions:

- The half-life, clearance, and volume of distribution of FIBRYNA following 70 mg/kg intravenous dose was 76 ± 24 hours, 0.66 ± 0.20 mL/hour per kg, and 70 ± 30 mL/kg, respectively. The half-life of FIBRYNA was about 7 hours longer and clearance was 17% slower than Haemocomplettan® P.

- The PK of FIBRYNA was not different between adults and adolescents. The half-life of FIBRYNA in adolescents was 72.8 ± 16.5 hours as compared to 76.9 ± 26.1 hours for the adults. The clearance of FIBRYNA was similar in both age groups (0.68 ± 0.18 and 0.66 ± 0.21 mL/hr per kg). Race (Caucasians vs Asians) and gender had no impact on the PK of FIBRYNA.

- The 90% confidence interval (CI) for the AUC indicated that FIBRYNA and Haemocomplettan® P were not bioequivalent (i.e., CIs were outside the acceptable range of 80 to 125% (123%-141%).

- The mean increase in MCF at 1-hour post-dose after FIBRYNA or Haemocomplettan® P administration from baseline (all with MCF of 0) was 9.7 ± 2.9 mm and 10 ± 4.3 mm, respectively.

7. Safety

The total safety population included 35 subjects (22 subjects in FORMA-01 and 13 subjects in FORMA-02) with CFD, of whom eight were 12 to <18 years of age. The sex distribution was 14 males and 21 females. The racial distribution was 23 White, 11 Asian, and one Other (Arab). There was a single Hispanic/Latino subject.

The safety data from FORMA-01 and FORMA-02 were pooled; however, the dose administered differs between the two studies. In FORMA-01, a fixed dose of 70 mg/kg was administered in non-bleeding subjects with congenital afibrinogenemia, whereas the dose administered in FORMA-02 was targeted to achieve plasma fibrinogen levels of 100 mg/dL (for minor bleeds) in subjects with both congenital hypo- and afibrinogenemia. The estimated fibrinogen plasma levels were 125 mg/dL at 4 hours in FORMA-01; the mean fibrinogen level was 116 mg/dL for all treatments of all 23 BEs in FORMA-02. However, given the extremely rare prevalence of CFD, it will be challenging to evaluate the safety of different ranges of plasma fibrinogen levels.

No subject discontinued a study due to an AE. There were no anti-fibrinogen antibody development and no deaths. The two AEs related to FIBRYNA were mild, including one event of pyrexia and one hypersensitivity reaction. Overall, based on FORMA-01 and FORMA-02, the safety profile of FIBRYNA is acceptable.

However, there are limitations to the safety data available from these studies. With the exception of one subject who underwent a surgical procedure for enucleation of the eye, and dosed to a target fibrinogen level of 150mg/dL, there were no treatments targeted to plasma fibrinogen levels of 150mg/dL to treat major BEs. To further assess the safety of the dose targeted to achieve a plasma fibrinogen level of 150 mg/dL, safety data for treatment of six minor BEs in FORMA-02 that resulted in target plasma fibrinogen level >140 mg/dL were analyzed. There were no thrombotic events, deaths, or discontinuations in subjects who achieved target fibrinogen levels >140mg/dL. The single subject who was dosed to 150 mg/dL for perioperative management (as described above) achieved a plasma fibrinogen level of 220 mg/dL, with no thrombotic event, death, or study discontinuation. Thus, there were a total of seven subjects evaluable to assess the safety of the target fibrinogen levels that approximated 150mg/dL. Of particular concern in subjects with congenital afbrinogenemia is the risk for paradoxical arterial and venous thrombosis, which may occur more often in subjects who receive multiple infusions of FRT for treatment of major bleeding and in the surgical setting with a target plasma fibrinogen level of 150 mg/dL (please see Background Section of this document).

The safety data, although sufficient to support marketing approval of FIBRYNA for the treatment of major bleeding, require additional characterization through a post-marketing study. Of interest in such a study would be the thrombotic risks associated with doses targeted to plasma fibrinogen levels of 150mg/dL, and following administration of multiple doses, as may be required for control of some cases of major bleeding.

Pharmacovigilance

Submitted data do not suggest any safety concerns after a single dose administration for minor bleeding in patients with congenital afibrinogenemia. A safety postmarketing study will be

required (PMR) under Section 505(o) to further characterize thrombotic risk after treatment with Fibryna for major bleeding.

8. Advisory Committee Meeting

The Office of Tissues and Advanced Therapies determined that referral to an Advisory Committee was not needed prior to licensure, for the following reasons:

- The drug is not the first in class. A relevant Blood Products Advisory Committee (BPAC) meeting regarding accelerated approval of RiaSTAP® was held on January 9, 2009.

- The mechanism of action of FIBRYNA and its role in blood coagulation are well understood.

- The manufacturing process of FIBRYNA is partially shared with other currently licensed plasma-derived products including Wilate, which is manufactured in the same facility.

- FIBRYNA is manufactured using only (b) (4) Plasma collected in FDA-approved plasma facilities. All donations comply with the requirements of 21 CFR 640.60.

- The manufacturing process of FIBRYNA includes two dedicated viral clearance steps: S/D treatment, and nanofiltration (Planova 20N or Pegasus SV4). No human or animal-derived materials are used in the manufacture and formulation of FIBRYNA. Thus, product safety with regard to adventitious viruses is assured.

- Serious AEs were not noted in FORMA-01 and FORMA-02, and the evaluation of the application did not raise unexpected and important safety issues.

- The clinical study design did not raise substantial review issues.

- FRT with fibrinogen concentrate is an accepted practice in the treatment of bleeding and perioperative management in CFD and to date has not posed significant public health questions.

- Review of information submitted in the BLA for FIBRYNA did not raise any controversial issues or pose unanswered scientific questions which would have benefited from Advisory Committee discussion and recommendations.

9. Other Relevant Regulatory Issues

The notable issues raised in the course of the review are described in the respective sections of this document, and they have been satisfactorily resolved through information requests and teleconferences. There were no other relevant regulatory issues.

10. Labeling

a) Proprietary Name

The proposed proprietary name for the product, FIBRYNA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) and was recommended to be acceptable on July 22, 2016. FIBRYNA was found acceptable as the proprietary name for the product by CBER on September 2, 2016.

b) Conclusions of APLB and Committee Review of Draft Package Insert and Other Labeling

The product labeling (i.e., prescribing information, patient package insert, and instructions for use) were reviewed, commented on, and/or revised by the appropriate discipline reviewers before APLB conducted its review from a promotional and comprehension perspective. CBER comments and recommendations regarding the product labeling and carton/vial labels were initially conveyed to Octapharma on May 26, 2017, and discussed through June 6, 2017.

Final versions of the product labeling (FPI) and labels, submitted to the BLA on May 31, 2017 (Container label) and June 6, 2017 (Package Insert and Carton label), are considered acceptable. A copy of FPI is attached.

11. Recommendation/Risk Benefit Assessment

a) Recommended Regulatory Action

The review committee recommends approval of this BLA. The manufacturing process for FIBRYNA, Fibrinogen (Human), is validated and adequately controlled. The clinical data for FIBRYNA provide substantial evidence of effectiveness and support a favorable benefit/risk determination for the use of FIBRYNA for adults and adolescents (≥ 12 years) with CFD, including afibrinogenemia and hypofibrinogenemia, for the treatment of acute bleeding episodes. FIBRYNA is not indicated for dysfibrinogenemia.

b) Benefit/Risk Assessment

FIBRYNA treatment results in replacement of plasma fibrinogen levels that control major and minor bleeding episodes in patients with congenital afibrinogenemia and hypofibrinogenemia.

The risks of FIBRYNA are hypersensitivity reactions and thrombosis. Although there were not thrombotic risks from FIBRYNA in the two studies, the anticipated risks of thrombosis of FIBRYNA relate to the risks associated with FRT.

Overall, the benefits described above outweigh the risks related to FIBRYNA for the proposed indication.

c) Recommendation for Postmarketing activities

The clinical trial data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS). FDA recommends the following for postmarket safety monitoring for FIBRYNA:

1) Routine pharmacovigilance including adverse event reporting under 21 CFR 600.80

2) Postmarketing Requirement (PMR) Under Section 505(o): Conduct a prospective observational study of patients ≥ 12 years of age with congenital afibrinogenemia and hypofibrinogenemia treated with FIBRYNA for at least 10 major BEs to further characterize the risk of thromboembolic events following FIBRYNA use.

Study timeline (proposed by the Applicant):

Final Protocol Submission: September 30, 2017
Study Completion Date: March 31, 2024
Final Report Submission: June 30, 2024

3) A post-marketing required study under the Pediatric Research Equity Act (PREA) to evaluate the safety and efficacy of FIBRYNA for the treatment of acute bleeding in children <12 years of age. This study, FORMA-04, is ongoing and includes evaluation of efficacy and safety of FIBRYNA for the management of acute bleeding (b) (4) . The PREA-related post-marketing requirement applies only to evaluation of safety and efficacy for the treatment of acute bleeding.

Study timeline (proposed by the Applicant):

Final protocol submission date: September 28, 2015
Study completion date: December 31, 2020
Complete study report submission date: June 30, 2021