Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Division of Epidemiology

Fibryna (Human Fibrinogen) BLA 125612
Pharmacovigilance Plan Review Memorandum

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Through:	Meghna Alimchandani, MD Chief, Pharmacovigilance Branch (PVB) Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE) Scott Proestel, MD Director, Division of Epidemiology (DE) Office of Biostatistics and Epidemiology (OBE)
To:	Ze Peng, PhD Chair, CMC Reviewer Office of Tissues and Advanced Therapies (OTAT)
Subject:	Pharmacovigilance Plan Review Memorandum
Applicant:	Octapharma Pharmazeutika Produktionsges
Proposed Trade Name:	Fibryna
BLA Submission:	Original BLA 125612/0
Proposed Indication:	Acute bleeding episodes (b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia
Action Due Date:	June 9, 2017

1.0 INTRODUCTION

1.1 Objectives/Scope

The sponsor, Octapharma, has submitted an original BLA 125612/0 seeking initial licensure for the product, human fibrinogen concentrate (proposed trade name, Fibryna), to be used as fibrinogen replacement therapy (FRT) for patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. The purpose of this review memorandum is to evaluate the sponsor's proposed plan for postmarketing safety monitoring and to identify potential safety concerns associated with the use of Fibryna that may need to be addressed through additional postmarketing safety surveillance, studies, or other pharmacovigilance activities, should the product be approved.

1.2 Product Description

Fibryna is a double virus-inactivated/eliminated, highly purified concentrate of freeze-dried fibrinogen manufactured from human plasma. Fibrinogen is a plasma-soluble protein and it is the key substrate for plasmatic blood coagulation and fibrinolysis. Fibrin is formed after thrombin cleavage of fibrinopeptide A from fibrinogen Aα chains, and this initiates fibrin polymerization. Double-stranded fibrils form associations, and concomitant lateral fibril associations and branching create a clot network. Fibrinogen deficiency and the resultant inability to form a clot can lead to massive hemorrhage in affected individuals.

Fibryna is distributed as a lyophilized cake to be reconstituted with sterile water. To reduce the risk of virus transmission, each blood plasma donation used for the manufacture of Fibryna is tested for antibodies to human immunodeficiency virus (HIV-1/2), hepatitis C virus (HCV), and hepatitis B virus (HBV) surface antigen (HBsAg). Each donation is also tested for hepatitis A virus (HAV) and Parvo B19-Virus genomes with (b) (4) test methods. Only plasma pools that are found negative for HBsAg, HCV-RNA, HIV-1 and HIV-2 antibodies are used for the manufacture of Fibryna. Additionally, two dedicated virus inactivation/removal steps, i.e. Solvent/Detergent (S/D) treatment and nanofiltration were introduced into the manufacturing process of Fibryna. S/D treatment inactivates enveloped viruses, and nanofiltration is used to target unenveloped viruses, such as parvovirus. Fibryna is presented as a combination product and is packaged with a reconstitution device, which is intended to (b) (4) .

Octajet Reconstitution Device: Fibryna is supplied as a lyophilized powder for reconstitution. A reconstitution device, "Octajet", designed by (b) (4) , is provided to (b) (4) The use of Octajet reduces the risk of (b) (4) .

1.3 Regulatory History

This is an original BLA submission seeking initial licensure for Fibryna in the U.S. There are no post-licensure materials for review, as the product has not been marketed in any country.

1.4 Proposed Indication

The proposed indication is for the treatment of acute bleeding episodes (b) (4)

(b) (4) in adult and pediatric patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia. Fibryna is not indicated for dysfibrinogenemia. Fibryna is indicated for intravenous use only, and must be reconstituted prior to use. Fibryna administration should be individualized based on the extent of bleeding, laboratory values and the clinical condition of the patient.

2.0 MATERIALS REVIEWED

Document Reviewed	Source
1.16.1 Risk Management Plan 5.3.5.3 Integrated Summary of Safety 2.5 Clinical Overview 1.14 Proposed labeling and proposed Package Insert	BLA 125612
Input from Clinical Reviewer	CBER staff

Pertinent published literature was also reviewed and is referenced in this memo.

3.0 DISEASE EPIDEMIOLOGY/BACKGROUND

The prevalence of congenital fibrinogen deficiency is approximately 1-2 per million in Western countries. Higher incidences are noted in countries where consanguineous marriage is practiced, such as the Middle East and Southern India. Congenital fibrinogen deficiency (afibrinogenemia) is an autosomal recessive disease resulting from mutations in any of the three genes that encode the three polypeptide chains of fibrinogen on chromosome 4. The majority of afibrinogenemia cases arise from mutations in the FGA gene. Failure to produce any of the individual peptide chains results in virtually complete absence of the mature protein. Eventually, the deficiency results in defects in the quality and quantity of circulating fibrinogen. Treatment options include replacement of fibrinogen with human fibrinogen concentrate, fresh frozen plasma or cryoprecipitate.

Afibrinogenemia frequently presents in the neonatal period, with up to 85% of cases presenting as bleeding from the umbilical cord. Bleeding can also occur in the skin, soft tissues, muscles, joints, gastrointestinal tract, or genitourinary tract. Intracranial hemorrhage is a major cause of mortality. Women with afibrinogenemia may suffer from recurrent, spontaneous first trimester abortions. However, the bleeding tendency is highly variable even with identical mutations.

4.0 SUMMARY OF CLINICAL TRIAL EXPOSURE

One completed clinical trial (FORMA-01) and one ongoing clinical trial, (FORMA-02) comprise the clinical experience with Fibryna. So far, 35 patients have been enrolled and treated in FORMA-01 and FORMA-02. An additional clinical trial recruiting only pediatric patients (FORMA-04) was started in December 2015. The aim of the third ongoing clinical trial (FORMA-04) is to assess the efficacy, safety and pharmacokinetics of Fibryna for on-demand treatment of acute bleeding episodes (b) (4) in pediatric patients with congenital fibrinogen deficiency.

5.0 SUMMARY OF CLINICAL SAFETY

Study FORMA-01 (N = 22)
FORMA-01 was a multinational, multicenter study in 22 non-bleeding subjects with congenital fibrinogen deficiency, comparing the PK of Fibryna with the licensed comparator, RiaSTAP. Patients were randomized to receive a single infusion of either Fibryna or RiaSTAP in two study periods. Safety data is presented in Table 1 below. Treatment-Emergent Adverse Events (TEAEs) during FORMA-01 were defined as AEs occurring up to day 14 post-administration in each study period. The data are 17 TEAEs (14 mild, 2 moderate, 1 severe) in 9 patients during the Fibryna period, and 22 TEAEs (21 mild, 1 moderate) in 9 patients during the RiaSTAP treatment period. One severe TEAE (urinary tract infection) occurred during the Fibryna treatment period, 6 days after infusion. This was considered by the investigator to be unrelated to the therapy. One TEAE of pyrexia was considered by investigator to be possibly related to therapy, but the event was mild and resolved spontaneously. One patient experienced 2 serious TEAEs (abdominal pain and vaginal hemorrhage) occurring 25 days after treatment. This was considered by the investigator to be unrelated to treatment, resolved and subject recovered. There were no cases of thromboembolism and no cases of allergic reaction. There was a single case of thrombophlebitis in patient (b) (6), mild in severity and considered to be unrelated by investigator. There were no deaths following either treatment.[1] There were no seroconversions for HIV, HAV, HBV, HCV or parvovirus B19 observed after infusion of any of the products.

Table 1: Clinical Safety data from Study FORMA-01[2]

	Fibryna	**RiaSTAP**
TEAEs	9 patients (40.9%),17 events	9 patients (40.9%), 22 events
Vertigo	0	1 (4.5%)
Gastrointestinal disorders (abdominal pain, diarrhea, dyspepsia, nausea, gingival bleeding, food poisoning)	3 (13.6%)	3 (13.6%)
General and administration (asthenia, pain, pyrexia)	3 (13.6%)	3 (13.6%)
Infection and infestation (nasopharyngitis, URI, UTI)	2 (9.1%)	2 (9.1%)
Injury, contusion, fall	2 (9.1%)	0
Metabolic (decreased appetite)	1 (4.5%)	0
Laboratory (ALT, AST, Hgb)	1 (4.5%)	2 (9.1%)
Musculoskeletal (arthralgia, myalgia, back, extremity pain)	1 (4.5%)	3 (13.6%)
Nervous system (headache, dizziness)	0	3 (13.6%)
Reproductive system (vaginal hemorrhage)	1 (4.5%)	0
Respiratory (cough)	0	1 (4.5%)
Vascular (Thrombophlebitis)[3]	1 (4.5%)	0

[1] Octapharma FORMA-01 clinical study report
[2] Octapharma FORMA-01 clinical study report
[3] Case of thrombophlebitis in patien(b) (6), mild in severity and considered to be not related by investigator.

Study FORMA-02 (N = 13)
FORMA-02 is an ongoing prospective, open-label, uncontrolled, Phase III study to assess the efficacy and safety of Fibryna for on-demand treatment of acute bleeding and to prevent bleeding during and after surgery in subjects with congenital fibrinogen deficiency. This study is ongoing, with a projected conclusion at Q3 2020. Data from interim analysis was available for:

- 13 subjects > 12 years old (11 adults, 2 adolescents)
- 22 minor bleeding episodes
- 4 subjects were treated for perioperative bleeding in minor surgeries

Hemostatic efficacy was assessed as successful in all bleeding episodes. Safety data is presented in Table 2 below. TEAEs were defined as AEs occurring up to day 14 post-administration. A total of 16 AEs were recorded in 7 patients (53.8%). Thirteen were TEAEs occurring in 7 patients. Of all the AEs, 13 were mild, 1 was moderate, and 2 were severe. One mild case of a skin reaction was assessed by the investigator as being possibly related to the study drug. Two severe and serious adverse events occurred in one patient. This patient suffered a patella fracture and ligament rupture in the left knee, which occurred due to a fall. These serious AEs were assessed by the investigator as being unrelated to the study drug.[4] Other TEAEs included gastrointestinal issues (constipation, vomiting and gingival bleeding). There were no deaths reported, no thrombotic events reported and no thromboembolic events reported. Immunogenicity was tested at day 1 and day 14, and 30 days after infusion. There was no development of anti-fibrinogen antibodies, although 2 subjects had such antibodies at study entry. The presence of the antibodies did not have any negative effect in these two subjects.[5]

Table 2: Clinical Safety data from Study FORMA-02[6]

PT, primary system organ class	**No. of patients, %, events**
Gastrointestinal (vomiting, constipation, gingival bleeding)	3 (23.1%)
Infection, infestation (Pharyngitis)	1 (7.7%)
Injury, poisoning, procedural (arthropod sting, incisional pain, ligament rupture, patella fracture, skin wound)	3 (23.1%) *arthropod sting 1 patient * ligament rupture, patella fracture 1 patient
Skin and subcutaneous disorders (drug eruption)	1 (7.7%)
Musculoskeletal (pain extremity)	1 (7.7%)
General and administrative (asthenia)	1 (7.7%)
Vascular (hemorrhage)	1 (7.7%)

Reviewer comment: Limitations of available data from this phase 3 study include: (a) lack of data on patients ≤ 12 years of age, (b) lack of data on acute major bleeding events, (c) lack of data on perioperative use in major surgery. Reviewer concurs on causality assessments by investigator. Please refer to the OTAT clinical review memorandum for additional discussion of clinical trial safety data.

[4] FORMA – II Report Body
[5] Report body FORMA-02 interim analysis/clinical study report
[6] FORMA – II Report Body

Octajet Reconstitution Device

Fibryna is supplied as a lyophilized powder for reconstitution. A reconstitution device, "Octajet" is provided to (b) (4) . Usability studies were performed to assess the adequacy of the Octajet together with the product; one in-house study with Octapharma employees was performed and one with representative users at a hospital. (b) (4) vials of batch (b) (4) were reconstituted and visually inspected by (b) (4) different technicians. In general, all users were able to follow the instructions and to perform critical tasks safely and effectively. No injuries occurred.[7] The target of the study, to evaluate the ability of the user to perform critical tasks as well as to understand the instruction for use, was successfully achieved. However, the (b) (4) was also assessed as too difficult and adjustments shall be implemented by (b) (4) before commercialization of the device.

6.0 LITERATURE REVIEW[8]

1. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood 2004; 104: 1243–52.
Reviewer comment: Review article of genetic basis, clinical manifestations and management of inherited coagulation disorders.

2. Acharya SS, Coughlin A, Dimichele DM, North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. J Thromb Haemost 2004; 2: 248–56.
Reviewer comment: Registry for rare bleeding disorders.

3. Lak M, Keihani M, Elahi F, Peyvandi F, Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenaemia. Br J Haematol 1999; 107: 204–6.
Reviewer comment: Bleeding symptoms in afibrinogenemia are qualitatively different and less severe than that of hemophilia.

4. Peyvandi F, Duga S, Akhavan S, Mannucci PM. Rare coagulation deficiencies. Haemophilia 2002; 8: 308–21.
Reviewer comment: Review article of clinical manifestations of rare coagulation deficiencies.

5. Peyvandi F, Haertel S, Knaub S, Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. J Thromb Haemost. 2006 Jul;4(7):1634-7.
Reviewer comment: Afibrinogenemia may be associated with symptoms that are unusual in patients with coagulation defects, such as thrombotic complication and miscarriage.

6. Thompson CA. FDA approves fibrinogen concentrate product. Am J Health Syst Pharm. 2009 Mar 1;66(5):428.

[7] 3.2.P.7 Usability specification and evaluation Octajet Transfer Device
[8] Comments on literature citations are reviewer comments.

Reviewer comment: Plasma derived fibrinogen product approved for treatment of patients with congenital fibrinogen deficiency.

7. Manco-Johnson MJ, Dimichele D, Castaman G, Fremann S, Knaub S, Kalina U, Peyvandi F, Piseddu G, Mannucci P; FIBRINOGEN CONCENTRATE STUDY GROUP. Pharmacokinetics and safety of fibrinogen concentrate. J Thromb Haemost. 2009 Dec;7(12):2064-9.
Reviewer comment: PK findings confirm rapid increase in plasma fibrinogen levels after infusion with fibrinogen concentrate.

8. Schenk B, Lindner AK, Treichl B et al. Fibrinogen supplementation ex vivo increases clot firmness comparable to platelet transfusion in thrombocytopenia. Br J Anesth. 2016 Nov;117(5):576-582.
Reviewer comment: Fibrinogen concentrate can improve clot firmness and offers good safety profile.

9. Fominskiy E, Nepomniashchikh VA, Lomivorotov VV, et al. Efficacy and Safety of Fibrinogen Concentrate in Surgical Patients: A Meta-Analysis of Randomized Controlled Trials. J Cardiothoracic Vasc Anesth. 2016 Oct;30(5):1196-204.
Reviewer comment: In surgical patients, FC was associated with reduced bleeding.

10. Oda T, Itoh H, Kawai K et al. Three successful deliveries involving a woman with congenital afibrinogenemia – conventional fibrinogen concentrate infusion vs. 'as required' fibrinogen concentrate infusion based on changes in fibrinogen clearance. Hemophilia. 2016 Sep; 22(5):e478-81.
Reviewer comment: Comparison of two different management strategies for afibrinogenemia during pregnancy.

11. Rottenstreich A, Lask A, Schliamser L, Zivelin A, et al. Thromboembolic events in patients with severe inherited fibrinogen deficiency. J Thromb Thrombolysis. 2016 42:261-266.
Reviewer comment: A high rate of paradoxical thrombosis has been reported in patients with severe afibrinogenemia.

12. Bornikova L, Peyvandi F, Allen G, et al. Fibrinogen replacement therapy for congenital fibrinogen deficiency. J Thrombosis and Haemostasis, 2011; 9:1687-704.
Reviewer comment: 104 papers were reviewed, a total of 50 cases identified, afibrinogenemia is associated with thromboembolic complications, with or without treatment.

13. Negrier C, Rothschild C, Borg JY, Lambert T, Claeyssens S et al. Post-authorization safety study of Clottafact, a triply secured fibrinogen concentrate in congenital afibrinogenemia. A prospective observational study. VoxSanguins 2016. 111, 383-390.
Reviewer comment: A new fibrinogen concentrate developed, post authorization safety study followed 14 patients for 1 year.

7.0 PHARMACOVIGILANCE PLAN REVIEW

Octapharma has proposed the following Pharmacovigilance Plan (PVP) for Fibryna:

Summary of Safety Concerns	
Important Identified Risks	• Hypersensitivity reactions, including anaphylactic reactions • Thromboembolic Events
Important Potential Risks	Suspected transmission of infectious agents
Missing Information	• Safety in elderly patients • Safety in pregnant or breast feeding women • Safety in patients with hepatic impairment

Risk Management Plan, Version 1, dated 03-May-2016; p. 35

7.1 Important Identified Risks

- Hypersensitivity reactions, including anaphylactic reactions
  - There was one allergic reaction reported in the clinical studies with Fibryna. It is recognized that allergic hypersensitivity reactions are a possible event.
  - Proposed label:
    Section 4.3, Contraindications: Hypersensitivity to the active substance or to any of the excipients.
    Section 4.4, Special warnings and special precautions for use: If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.
    Section 4.8, Undesirable effects: Allergic or anaphylactic-type reactions are mentioned in the table of undesirable effects.
- Thromboembolic events
  - There were no thromboembolic events (TEE) reported in the studies conducted. As per Octapharma, TEE is recognized as a rare, but possible event for this product class.
  - Proposed label:
    Section 4.4 Special warnings and special precautions for use
    There is a risk of thrombosis when patients, with either congenital or acquired deficiency, are treated with human fibrinogen, particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.
    In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in peri- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human plasma fibrinogen should be weighed against the risk off thromboembolic complications. Caution and close monitoring should also be performed.

Section 4.8 Undesirable effects

Thromboembolic episodes (including myocardial infarction and pulmonary embolism) are listed as undesirable effects.

Reviewer comment: Should this product be approved, FDA will require a postmarket study for collection of additional data to further characterize the risk of TEE after treatment with Fibryna for major bleeding. Please see section 7.5 for discussion of this PMR

7.2 Important Potential Risks

- Suspected transmission of infectious agents
  - There were no transmissions reported in the clinical studies. Risk minimization measures include two dedicated virus inactivation/removal steps, i.e. Solvent/Detergent (S/D) treatment and nanofiltration. Additionally, each blood plasma donation used for the manufacture of Fibryna is tested for antibodies to human immunodeficiency virus (HIV-1/2), hepatitis C virus(HCV), and hepatitis B virus (HBV) surface antigen(HBsAg). Each donation is tested for hepatitis A virus (HAV), HBV, HCV, HIV, and Parvo B19-Virus genomes with (b) (4) test methods. Additional (b) (4) tests on production pools are performed as defined in the respective marketing authorization. Only plasma pools that are found negative for HBsAg, HCV-RNA, HIV-1 and HIV-2 antibodies are used for the manufacture of Fibryna.
  - Proposed label:

    Section 4.4, Special warnings and precautions for use

    Virus safety

    The possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. hemolytic anemia). Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived fibrinogen concentrates.

7.3 Important Missing Information/Limitations

- Safety in elderly patients
- Safety in pregnant or breast feeding women
- Safety in patients with hepatic impairment

7.4 Potential for off-label use

There is a potential for off-label use in acquired fibrinogen deficiency. Haemocomplettan P, a licensed fibrinogen concentrate, is approved for this indication in the EU. Additionally, there have been a small number of studies examining the use of fibrinogen concentrate for control of bleeding in cardiovascular surgery, trauma, burns, liver transplant and orthopedic surgery.[9]

[9] 1.16.1 Risk Management

7.5 Pharmacovigilance Actions

The sponsor proposes routine pharmacovigilance for postmarket safety monitoring, should the product be approved. Routine pharmacovigilance monitoring will include the submission of all serious, unexpected (unlabeled) AE reports to FDA within 15 days (expedited reporting) and the quarterly submission of Periodic Adverse Experience Reports (PAERs) for the first 3 years after licensure. Routine pharmacovigilance also includes continuous monitoring of the safety profile including signal detection, issue evaluation, updating labeling as necessary, and liaison with regulatory authorities.

In addition to routine surveillance, OBE/DE recommends a required postmarketing study (PMR) to further characterize thrombotic risk after Fibryna use in major bleeding events. The risk of TEE after Fibryna use and the need for a PMR was discussed at an interoffice OBE/OTAT Safety Assessment Meeting on April 5 and April 18, 2017 and at the Center level Safety Working Group on May 11, 2017.

Justification for PMR:

Fibryna is a human fibrinogen concentrate to be used as fibrinogen replacement therapy (FRT) in patients with congenital fibrinogen deficiency. This is a rare disease (approximate prevalence of 1 in one million) and the clinical safety database included 35 patients. Interim analysis from an ongoing clinical trial (N = 13) included treatment of 22 minor bleeding events. The safety and efficacy data from the clinical trials supporting licensure are adequate to support a marketing approval of Fibryna for the treatment of both minor and major bleeding. There were no thromboembolic events (TEE) in the clinical trials for Fibryna, including in subjects dosed to plasma fibrinogen levels proposed for the treatment of major bleeding. However, the clinical trial sample size was limited for this rare disease and most patients in the trials experienced minor bleeds. Studies and case reports in the published literature [REF 1 – 12] suggest an increased risk of TEE after FRT in patients with congenital afibrinogenemia and hypofibrinogenemia. As an FRT product, the TEE risk in the published literature represents a signal of a serious risk for Fibryna as well, and if present, such a risk would increase with the higher dose levels used for major bleeding. Therefore, collection of additional data in the postmarket setting is required to further characterize the risk of TEE after treatment with Fibryna for major bleeding.

Proposed language for Approval Letter:

POSTMARKETING REQUIREMENTS UNDER SECTION 505(o)
Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of the serious risk of thromboembolic events related to the use of Fibryna.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, we have determined that you are required to conduct the following study:

PMR #1: Conduct a prospective observational study of patients ≥12 years of age with congenital afibrinogenemia and hypofibrinogenemia treated with Fibryna for at least 10 major bleeding events to further characterize the risk of thromboembolic events following Fibryna use.
We acknowledge the timetable you submitted on May 5, 2017, which states that you will conduct this study according to the following schedule:

Final Protocol Submission: September 2017
Study Completion Date: 1 Quarter 2024
Final Report Submission: June 2024

PMR Study design: To fulfill this PMR, Octapharma has proposed a prospective multicenter, observational, one-arm study:

- Primary Objective – characterize TEE incidence in on-demand treatment of major bleeding with Fibryna
- Minimum number of acute major bleeding events – 10
- Sample size – 25 patients with congenital afibrinogenemia or hypofibrinogenemia
  As per the sponsor, "*The aim is to enroll up to 25 patients treated with Fibryna over the course of 6 years, in order to describe 105 bleeding events…10 are major bleeding events*."
  Sponsor rationale for sample size – Literature suggests that the incidence of bleeding symptoms in patients with congenital afibrinogenemia is expected to be about 0.7 bleeding events per year.[10] If 25 patients are included in the study world-wide, about 17.5 bleeding episodes may be expected per year. During a study duration of 6 years, about 105 bleeding episodes might be expected, including 10 major bleeding events. The sponsor also agrees to extend the study duration if the goal enrollment of 25 patients or 10 major bleeding events is not achieved in 6 years.
- Follow-up: All bleeding events will be followed up for a period of up to 28 days after treatment. Hospitalized patients will receive daily assessments. In the outpatient setting, patients will be contacted at 1 week and 4 weeks after treatment by a study nurse in a telephone interview.

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

8. CONCLUSION

The submitted safety data for Fibryna is limited by small sample size and lack of data on treatment of acute major bleeding events at the recommended target fibrinogen plasma level of 150 mg/dL. Literature suggests that there may be increased thrombotic risk after use of FRT.

[10] Peyvandi et al. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. J Thromb Haemost. 2006 Jul;4(7):1634-7

Should the product be licensed, a safety postmarketing study will be required to further characterize thrombotic risk with Fibryna use. Final determination of the benefit/risk profile of Fibryna is pending the addition of final clinical, statistical and product reviews.

9. RECOMMENDATIONS

The submitted clinical trial data does not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy (REMS). Should this product be approved, OBE/DE 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 bleeding events to further characterize the risk of thromboembolic events following Fibryna use.

Study timeline (proposed by Octapharma):

Final Protocol Submission	September 2017
Study Completion Date	1 Quarter 2024
Final Report Submission	June 2024

References

1. Mannucci PM, Duga S, Peyvandi F. Recessively inherited coagulation disorders. Blood 2004; 104: 1243–52.
2. Acharya SS, Coughlin A, Dimichele DM, North American Rare Bleeding Disorder Study Group. Rare Bleeding Disorder Registry: deficiencies of factors II, V, VII, X, XIII, fibrinogen and dysfibrinogenemias. J Thromb Haemost 2004; 2: 248–56.
3. Lak M, Keihani M, Elahi F, Peyvandi F, Mannucci PM. Bleeding and thrombosis in 55 patients with inherited afibrinogenaemia. Br J Haematol 1999; 107: 204–6.
4. Peyvandi F, Duga S, Akhavan S, Mannucci PM. Rare coagulation deficiencies. Haemophilia 2002; 8: 308–21.
5. Peyvandi F, Haertel S, Knaub S, Mannucci PM. Incidence of bleeding symptoms in 100 patients with inherited afibrinogenemia or hypofibrinogenemia. J Thromb Haemost. 2006 Jul;4(7):1634-7.
6. Thompson CA. FDA approves fibrinogen concentrate product. Am J Health Syst Pharm. 2009 Mar 1;66(5):428.
7. Manco-Johnson MJ, Dimichele D, Castaman G, Fremann S, Knaub S, Kalina U, Peyvandi F, Piseddu G, Mannucci P; FIBRINOGEN CONCENTRATE STUDY GROUP. Pharmacokinetics and safety of fibrinogen concentrate. J Thromb Haemost. 2009 Dec;7(12):2064-9.
8. Schenk B, Lindner AK, Treichl B et al. Fibrinogen supplementation ex vivo increases clot firmness comparable to platelet transfusion in thrombocytopenia. Br J Anesth. 2016 Nov;117(5):576-582.
9. Oda T, Itoh H, Kawai K et al. Three successful deliveries involving a woman with congenital afibrinogenemia – conventional fibrinogen concentrate infusion vs. 'as required' fibrinogen concentrate infusion based on changes in fibrinogen clearance. Hemophilia. 2016 Sep; 22(5):e478-81.
10. Rottenstreich A, Lask A, Schliamser L, Zivelin A, et al. Thromboembolic events in patients with severe inherited fibrinogen deficiency. J Thromb Thrombolysis. 2016 42:261-266.
11. Bornikova L, Peyvandi F, Allen G, et al. Fibrinogen replacement therapy for congenital fibrinogen deficiency. J Thrombosis and Haemostasis, 2011; 9:1687-704.
12. Negrier C, Rothschild C, Borg JY, Lambert T, Claeyssens S et al. Post-authorization safety study of Clottafact, a triply secured fibrinogen concentrate in congenital afibrinogenemia. A prospective observational study. VoxSanguins 2016. 111, 383-390.